National Institute for Health and Care Excellence

Draft

Venous thromboembolism in over 16s

Reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism

NICE guideline

Appendices A – I

October 2017

Draft for consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Contents

Appendices 5
Appendix A: Scope 5
Appendix B: Declarations of interest 17
Appendix C: Clinical review protocols 43
Appendix D: Health economic review protocol 135
Appendix E: Clinical study selection 137
Appendix F: Health economic study selection 140
Appendix G: Literature search strategies 141
Appendix H: Clinical evidence tables 155
Appendix I: References 960

Appendices

Appendix A: Scope

FINAL VERSION

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Guideline scope

Venous thromboembolism in people aged 16 and over: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism

Topic

This guideline will update the NICE guideline on Venous thromboembolism in adults admitted to hospital (CG92) as set out in the update decision.

For more information about why this guideline is being developed, and how the guideline will fit into current practice, see the context section.

Who the guideline is for

- People using services, families and carers and the public
- Healthcare professionals in the primary and secondary sectors
- Clinical commissioning groups

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive.

Equality considerations

NICE has carried out an equality impact assessment during scoping. The assessment:

- lists equality issues identified, and how they have been addressed
- explains why any groups are excluded from the scope.

The guideline will look at inequalities relating to heparin which is derived from the tissue of pigs or cattle. If recommended we will need to ensure that people

with religious or personal beliefs about the use of animal-derived products are given the opportunity to express their concerns and to receive information about alternative options.

1 What the guideline is about

1.1 Who is the focus?

Groups that will be covered

- Adults and young people (16 years and older) admitted to hospital.
- Adults and young people (16 years and older) discharged from hospital (including from A&E) with lower-limb devices such as plaster casts and braces.
- Adults and young people (16 years and older) attending hospital for day procedures including cancer treatment and surgery.
- Adults and young people (16 years and older) with psychiatric illness admitted to community mental health hospitals or units.
- Special consideration will be given to:
  - pregnant women admitted to hospital and midwife units including up to 6 weeks after giving birth
  - people in whom pharmacological prophylaxis is contraindicated **(new area)**
  - people in whom mechanical prophylaxis is contraindicated **(new area)**
  - people already using anticoagulants in whom bridging prophylaxis is required for VTE prophylaxis. **(new area)**
  - people using antiplatelets for cardiovascular disease. **(new area)**
  - people who are obese
  - people who have kidney disease

Groups that will not be covered

- People with suspected or confirmed venous thromboembolism (VTE).

FINAL VERSION

1.2 Settings

Settings that will be covered

- Primary and community care when continuing prophylaxis after hospital discharge.
- Secondary care.

Settings that will not be covered

- Community settings and hospices, except when continuing prophylaxis that has been started in hospital.

1.3 Activities, services or aspects of care

Key areas that will be covered

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

Areas from the published guideline that will be updated

1. Risk assessment
   - Patient risk factors for venous thromboembolism (VTE)
2. Methods of prophylaxis for reducing the incidence of VTE:
   - Mechanical prophylaxis including anti-embolism stockings (above or below the knee), intermittent pneumatic compression devices (full leg or below the knee), foot impulse devices, electrical stimulation, continuous passive motion and vena caval filters
   - Pharmacological prophylaxis including aspirin, dabigatran, fondaparinux, unfractionated heparin, low molecular weight heparin (LMWH), rivaroxaban and vitamin k antagonists [for example warfarin])
   - Timing of prophylaxis
   - Duration of prophylaxis

FINAL VERSION

3. Information and support
   - Content of information on prophylaxis methods and VTE provided to patients and their family members or carers.

Areas not in the published guideline that will be included in the update

1. Risk assessment
   - Risk prediction tools (for bleeding or VTE)
   - Reassessment of risk
2. Methods of prophylaxis
   - New interventions (for example apixaban and geko devices)
   - Bridging prophylaxis
   - Prophylaxis for patients already prescribed antiplatelet agents for cardiovascular disease

Areas that will not be covered

Areas from the published guideline that will not be updated

1 Methods of prophylaxis
   - Early mobilisation and leg exercises
   - Physiotherapy
   - Hydration
   - Regional compared with general anaesthetic.

Areas from the published guideline that will be removed

1. Methods of prophylaxis
   - Leg elevation

Areas not covered by the published guideline or the update

1. Secondary prevention of VTE

Recommendations in areas that are not being updated may be edited to ensure that they meet current editorial standards, and reflect the current policy and practice context.

FINAL VERSION

1.4 Economic aspects

We will take economic aspects into account when making recommendations. We will develop an economic plan that states for each review question (or key area in the scope) whether economic considerations are relevant, and if so whether this is an area that should be prioritised for economic modelling and analysis. We will review the economic evidence and carry out economic analyses, using an NHS and personal social services (PSS) perspective, as appropriate.

1.5 Key issues and questions

While writing this scope we have identified the following key issues, and key questions related to them. The term 'VTE' in this section refers to both deep vein thrombosis (DVT) and pulmonary embolism (PE):

1. Risk assessment:
   1.1 What is the accuracy of individual risk assessment or prediction tools in predicting the likelihood of VTE in patients who are admitted to hospital?
   1.2 What is the accuracy of individual risk assessment or prediction tools in predicting the likelihood of VTE in patients who are having day procedures (including surgery and chemotherapy) at hospital?
   1.3 What is the accuracy of individual risk assessment or prediction tools in predicting the likelihood of VTE in pregnant women who are admitted to hospital or midwife units?
   1.4 What is the accuracy of individual risk assessment or prediction tools in predicting the likelihood of major bleeding or the risk of bleeding in patients who are admitted to hospital?
   1.5 What is the accuracy of individual risk assessment or prediction tools in predicting the likelihood of major bleeding or the risk of in patients who are having day procedures (including surgery and chemotherapy) at hospital?
   1.6 What is the accuracy of individual risk assessment or prediction tools in predicting the likelihood of major bleeding or the risk of bleeding in pregnant women who are admitted to hospital or midwife units?

FINAL VERSION

1.7 How clinically and cost effective are risk assessment or prediction tools at reducing the rates of VTE in patients who are admitted to hospital?

1.8 How clinically and cost effective are risk assessment or prediction tools at reducing the rates of VTE in patients who are having day procedures (including surgery and chemotherapy) at hospital?

1.9 How clinically and cost effective are risk assessment or prediction tools at reducing the rates of VTE in pregnant women who are admitted to hospital or midwife units?

1.10 How effective is reassessment of patients who are admitted to or having day procedures at hospital?

If appropriate evidence is not identified from the questions above (1.1 to 1.10) the following 2 questions may also be considered:

1.11 What are the individual risk factors for VTE in patients who are admitted to hospital?

1.12 What are the individual risk factors for VTE in patients who are having day procedures (including surgery and chemotherapy) at hospital?

1.13 What are the individual risk factors for VTE in pregnant women who are admitted to hospital or midwife units?

2. Prophylaxis:

Each of the following questions will investigate individual populations separately. Populations include:

- people having the following types of surgery:
  - elective hip surgery
  - elective knee surgery
  - hip fracture
  - knee arthroscopy
  - other orthopaedic surgery
  - abdominal surgery (bariatric, liver, gastrointestinal, gynaecological, laparoscopic, thoracic and urological)

FINAL VERSION

  - cranial surgery
  - spinal surgery
  - cardiac surgery
  - vascular surgery
  - dental/maxillofacial surgery
  - vaginal surgery
- people discharged with lower-limb immobilisation (including boots, braces, Plaster of Paris [POP] and other devices)
- people being treated for:
  - major trauma
  - spinal injury
  - stroke
  - acute coronary syndromes
  - cancer
- people attending hospital as medical admissions
- people with central venous catheters
- people having palliative care
- pregnant women and up to 6 weeks after giving birth
- people with psychiatric disorders
- people who are obese
- people with kidney disease.

Each of the questions will consider the following settings, if appropriate: people in hospital and those having day procedures (including surgery, chemotherapy)

Each of the questions will include the following prophylaxis methods, if applicable:

- mechanical prophylaxis, including:
  - anti-embolism stockings (above or below knee)
  - intermittent pneumatic compression devices (full leg or below knee)
  - foot impulse devices
  - electrical stimulation (including geko devices)

FINAL VERSION

  - continuous passive motion
  - vena caval filters.

- pharmacological prophylaxis, including:
  - apixaban
  - aspirin
  - dabigatran
  - fondaparinux
  - unfractionated heparin
  - low molecular weight heparin (LMWH)
  - rivaroxaban
  - vitamin k antagonists (for example warfarin).

2.1 What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination)?
2.2 What is the effectiveness of vena caval filters in people admitted to hospital who are at high risk of DVT or PE admitted to hospital?
2.3 What is the most effective timing for starting prophylaxis with LMWH for people having surgery?
2.4 What is the most effective prophylaxis duration (covering the time in hospital only or continuing after discharge)?
2.5 What is the most effective prophylaxis strategy for inpatients in whom pharmacological prophylaxis is contraindicated?
2.6 What is the most effective prophylaxis strategy for inpatients in whom mechanical prophylaxis is contraindicated?
2.7 What is the most effective prophylaxis strategy for patients in whom both mechanical and pharmacological prophylaxis are contraindicated?
2.8 What is the most effective VTE prophylaxis strategy for bridging patients who are already using anticoagulants agents for other reasons?
2.9 What is the most effective VTE prophylaxis strategy in managing patients who are already using antiplatelets for cardiovascular disease?
2.10 What is the most effective VTE prophylaxis strategy for pregnant women admitted to hospital or a midwifery-led unit during labour?

FINAL VERSION

3. Information for patients, family members and carers:
   3.1 What specific information should be provided to people who need VTE prophylaxis?
   3.2 What information do patients, their family members and carers say they want about VTE prophylaxis?

1.6 Main outcomes

The main outcomes that will be considered when searching for and assessing the evidence are:

1. All-cause mortality
2. Pulmonary embolism
3. Fatal pulmonary embolism
4. Deep vein thrombosis (symptomatic or asymptomatic)
5. Major bleeding
6. Fatal bleeding
7. Heparin-induced thrombocytopenia
8. Post-thrombotic syndrome
9. Pulmonary hypertension
10. Quality of life (validated scores)
11. Hospital length of stay
12. Readmission
13. Neurological events (for example haemorrhagic stroke)

2 Links with other NICE guidance, NICE quality standards and NICE Pathways

2.1 NICE guidance

- Venous thromboembolism in adults admitted to hospital: reducing the risk (2010) NICE guideline CG92
- Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing (2012) NICE clinical guideline 144
- Caesarean section (2011) NICE clinical guideline 132

- Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) (2008) NICE clinical guideline 68.
- Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (2012) NICE technology appraisal 245
- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (2008) NICE technology appraisal 157.
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (2009) NICE technology appraisal 170
- The geko device for reducing the risk of venous thromboembolism (2014) NICE medical technology guidance 19.

NICE guidance that will be updated by this guideline

- Venous thromboembolism in adults admitted to hospital: reducing the risk (2010) NICE guideline CG92

NICE guidance about the experience of people using NHS services

NICE has produced the following guidance on the experience of people using the NHS. This guideline will not include additional recommendations on these topics unless there are specific issues related to VTE:

- Patient experience in adult NHS services (2012) NICE guideline CG138
- Service user experience in adult mental health (2011) NICE guideline CG136
- Medicines adherence (2009) NICE guideline CG76

2.2 NICE quality standards

NICE quality standards that may need to be revised or updated when this guideline is published

- Venous thromboembolism prevention (2010) NICE quality standard 3.

2.3 NICE Pathways

When this guideline is published it will update the existing NICE pathway on venous thromboembolism. NICE Pathways bring together all related NICE

guidance and associated products on a topic in an interactive topic-based flow chart.

3 Context

3.1 Key facts and figures

Hospital acquired venous thromboembolism, also known as hospital acquired thrombosis (HAT), covers all venous thromboembolism (VTE) that occurs in hospital and for 90 days after a hospital admission. Epidemiological studies have shown that HAT accounts for somewhere between 50-60% of all VTE seen. Hospital Episode Statistics showed that in 2013–14 there were 24,725 admissions for pulmonary embolism and 19,463 for DVT in England, resulting in 205,448 and 67,028 bed-days and 47,594 and 25,958 finished consultant episodes respectively. In 2013, in England and Wales there were 2,191 deaths recorded as due to pulmonary embolism (PE) and 2,816 due to deep vein thrombosis (DVT), but the actual number of people dying from these conditions is likely to be higher because of misdiagnosis and the failure to recognise VTE as the underlying cause. Thus hospital-acquired VTE accounts for thousands of deaths annually in the UK.

3.2 Current practice

In 2010, the CQUIN target introduced a payment linked to at least 90% of adults being risk assessed on admission to hospital. Figures reporting the uptake of some of the recommendations in CG92 are reported on NICE's website. Recent evidence also estimates that the national mortality rate from VTE has fallen by 8–9% since the recommendations in CG92 were introduced.

In addition, since the publication of the last version of the guideline, CG92, two new interventions for preventing venous thromboembolism (VTE) have become available: apixaban and geko devices.

FINAL VERSION

3.3 Policy, legislation, regulation and commissioning

Policy

The National VTE prevention programme was launched in England in 2010 by the Department of Health. This included the mandatory VTE risk assessment of 90% (later increased to 95%) of all people admitted to hospital. A risk assessment tool was created by the Department of Health and this was incorporated into the last version of this guideline. Risk assessment will be a key part of this update.

4 Further information

Registered stakeholders were consulted with on the draft scope between 11 December 2015 and 20 January 2016.

The guideline is expected to be published in February 2018.

You can follow progress of the guideline.

Our website has information about how NICE guidelines are developed.

Appendix B: Declarations of interest

The September 2014 version of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

Peter Barry (Chair from April 2017)

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (02.03.2016)	Not yet recruited	N/A	N/A
Second meeting (22.04.2016)	Not yet recruited	N/A	N/A
Third meeting (01.06.2016)	Not yet recruited	N/A	N/A
Fourth meeting (20.07.2016)	Not yet recruited	N/A	N/A
Fifth meeting (16.09.2016)	Not yet recruited	N/A	N/A
Sixth meeting (19.10.2016)	Not yet recruited	N/A	N/A
Seventh meeting (01.12.2016)	Not yet recruited	N/A	N/A
Eight meeting (05.01.2017)	Not yet recruited	N/A	N/A
Ninth meeting (08.02.2017)	Not yet recruited	N/A	N/A
Tenth meeting (09.02.2017)	Not yet recruited	N/A	N/A
Eleventh meeting (15.03.2017)	Not yet recruited	N/A	N/A
Twelfth meeting (19.04.2017)	None	N/A	N/A
Thirteenth meeting (25.05.2017)	None	N/A	N/A
Fourteenth meeting	None	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
(26.05.2017)			
Fifteenth meeting (22.06.2017)	Attended an educational meeting on the subject of paediatric critical care transport, where the company CareFusion sponsored room hire, lunch and mid - afternoon refreshments. The meeting was not about Venous ThromboEmbolism, and as far as I am aware, CareFusion do not market any of the interventions under consideration by the committee. I was not paid to attend the meeting.	Personal non-financial non-specific	Declare and participate
Sixteenth meeting (28.07.2017)	No change to existing declarations	N/A	N/A
Seventeenth meeting (07.12.2017)			

5 **Jagjot Chahal**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (02.03.2016)	Not yet recruited	N/A	N/A
Second meeting (22.04.2016)	Not yet recruited	N/A	N/A
Third meeting (01.06.2016)	None	N/A	N/A
Fourth meeting (20.07.2016)	None	N/A	N/A
Fifth meeting (16.09.2016)	None	N/A	N/A
Sixth meeting (19.10.2016)	None	N/A	N/A
Seventh meeting (01.12.2016)	None	N/A	N/A
Eight meeting	None	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
(05.01.2017)			
Ninth meeting (08.02.2017)	None	N/A	N/A
Tenth meeting (09.02.2017)	None	N/A	N/A
Eleventh meeting (15.03.2017)	None	N/A	N/A
Twelfth meeting (19.04.2017)	Abstract accepted for the ISTH 2017 conference on the safety and cost-effectiveness of LMWH in comparison to NOACs for treatment indications.	Personal non-financial specific	Declare and participate
Thirteenth meeting (25.05.2017)	No change to existing declarations.	N/A	N/A
Fourteenth meeting (26.05.2017)	No change to existing declarations	N/A	N/A
Fifteenth meeting (22.06.2017)	No change to existing declarations	N/A	N/A
Sixteenth meeting (28.07.2017)	Publication of a CPD learning article in the Pharmaceutical Journal: Heparin-induced thrombocytopenia.	Personal non-financial specific	Declare and participate
Seventeenth meeting (07.12.2017)			

6 **Deepak Chandra**

Committee meeting	Declaration of interest	Classification	Action taken
On application	None	N/A	N/A
First meeting (02.03.2016)	No change to existing declarations	N/A	N/A
Second meeting (22.04.2016)	No change to existing declarations	N/A	N/A
Third meeting (01.06.2016)	Pharmaceutical company support for venue hire, catering cost and keynote speaker for launch of thrombosis and anticoagulation services.	Non-personal financial specific	Declare and participate

Committee meeting	Declaration of interest	Classification	Action taken
Fourth meeting (20.07.2016)	No change to existing declarations	N/A	N/A
Fifth meeting (16.09.2016)	No change to existing declarations	N/A	N/A
Sixth meeting (19.10.2016)	No change to existing declarations	N/A	N/A
Seventh meeting (01.12.2016)	No change to existing declarations	N/A	N/A
Eight meeting (05.01.2017)	No change to existing declarations	N/A	N/A
Ninth meeting (08.02.2017)	No change to existing declarations	N/A	N/A
Tenth meeting (09.02.2017)	No change to existing declarations	N/A	N/A
Eleventh meeting (15.03.2017)	No change to existing declarations	N/A	N/A
Twelfth meeting (19.04.2017)	No change to existing declarations	N/A	N/A
Thirteenth meeting (25.05.2017)	Apologies received	N/A	N/A
Fourteenth meeting (26.05.2017)	No change to existing declarations	N/A	N/A
Fifteenth meeting (22.06.2017)	Participation in APEX study as a site investigator. Did not have any role in design of study or data review and final publication Betrixaban was not included in any review protocol for this guideline.	Personal non-financial non-specific	Declare and participate
Sixteenth meeting (28.07.2017)	Apologies received	N/A	N/A
Seventeenth meeting (07.12.2017)			

7 **Sarah Chissell (obstetric subgroup member)**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (14.03.2017)	None	N/A	N/A
Second meeting (24.05.2017)	None	N/A	N/A

8 **Ian Donald**

Committee meeting	Declaration of interest	Classification	Action taken
On application	Took part in a medical advisory panel for Vifor Pharmaceuticals in 2015. Secondary Care Member of the Board for Bristol Clinical Commissioning Group.	Personal financial non-specific	Declare and participate
First meeting (02.03.2016)	No change to existing declarations	N/A	N/A
Second meeting (22.04.2016)	No change to existing declarations	N/A	N/A
Third meeting (01.06.2016)	No change to existing declarations	N/A	N/A
Fourth meeting (20.07.2016)	No change to existing declarations	N/A	N/A
Fifth meeting (16.09.2016)	No change to existing declarations	N/A	N/A
Sixth meeting (19.10.2016)	No change to existing declarations	N/A	N/A
Seventh meeting (01.12.2016)	No change to existing declarations	N/A	N/A
Eight meeting (05.01.2017)	No change to existing declarations	N/A	N/A
Ninth meeting (08.02.2017)	No change to existing declarations	N/A	N/A
Tenth meeting (09.02.2017)	No change to existing declarations	N/A	N/A
Eleventh meeting	No change to existing declarations	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
(15.03.2017)			
Twelfth meeting (19.04.2017)	No change to existing declarations	N/A	N/A
Thirteenth meeting (25.05.2017)	Apologies received.	N/A	N/A
Fourteenth meeting (26.05.2017)	No change to existing declarations	N/A	N/A
Fifteenth meeting (22.06.2017)	No change to existing declarations	N/A	N/A
Sixteenth meeting (28.07.2017)	No change to existing declarations	N/A	N/A
Seventeenth meeting (07.12.2017)			

9 **Xavier Griffin**

Committee meeting	Declaration of interest	Classification	Action taken
On application	Co-editor Bone Joint and Musculoskeletal Trauma Cochrane Group with multiple systematic reviews in trauma surgery.	Personal non-financial specific	Declare and participate
	Grants (paid to University) from X-Bolt Orthopaedics for two investigator-initiated, industry funded randomised trials testing a novel implant for hip fracture fixation.	Non-personal financial non-specific	Declare and participate
	Grant from Orthodynamics (paid to University) for investigator-initiated, industry-funded randomised trials testing a novel implant for total hip arthroplasty for fracture.	Non-personal financial non-specific	Declare and participate
	NIHR RfPB grant (paid to NHS Trust) for a randomised trial testing alternative arthroplasties for hip fracture.	Non-personal financial non-specific	Declare and participate
First meeting (02.03.2016)	No change to existing declarations	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
Second meeting (22.04.2016)	No change to existing declarations	N/A	N/A
Third meeting (01.06.2016)	No change to existing declarations	N/A	N/A
Fourth meeting (20.07.2016)	No change to existing declarations	N/A	N/A
Fifth meeting (16.09.2016)	No change to existing declarations	N/A	N/A
Sixth meeting (19.10.2016)	No change to existing declarations	N/A	N/A
Seventh meeting (01.12.2016)	No change to existing declarations	N/A	N/A
Eight meeting (05.01.2017)	No change to existing declarations	N/A	N/A
Ninth meeting (08.02.2017)	No change to existing declarations	N/A	N/A
Tenth meeting (09.02.2017)	No change to existing declarations	N/A	N/A
Eleventh meeting (15.03.2017)	Joining lower limb immobilisation modelling study for HTA as a stakeholder member. Study not yet started. https://www.sheffield.ac.uk/scharr/sections/hsr/cure/projects/tilli	Non-personal financial specific	Declare and participate
Twelfth meeting (19.04.2017)	No change to existing declarations	N/A	N/A
Thirteenth meeting (25.05.2017)	No change to existing declarations	N/A	N/A
Fourteenth meeting (26.05.2017)	No change to existing declarations	N/A	N/A
Fifteenth meeting (22.06.2017)	No change to existing declarations	N/A	N/A
Sixteenth meeting	No change to existing declarations	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
(28.07.2017)			
Seventeenth meeting (07.12.2017)			

10 **Nihal Gurusinghe (co-opted member)**

Committee meeting	Declaration of interest	Classification	Action taken
Eight meeting (05.01.2017)	None	N/A	N/A
Twelfth meeting (19.04.2017)	None	N/A	N/A

11

12 **Elizabeth Houghton**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (02.03.2016)	None	N/A	N/A
Second meeting (22.04.2016)	None	N/A	N/A
Third meeting (01.06.2016)	None	N/A	N/A
Fourth meeting (20.07.2016)	None	N/A	N/A
Fifth meeting (16.09.2016)	None	N/A	N/A
Sixth meeting (19.10.2016)	None	N/A	N/A
Seventh meeting (01.12.2016)	None	N/A	N/A
Eight meeting (05.01.2017)	None	N/A	N/A
Ninth meeting (08.02.2017)	None	N/A	N/A
Tenth meeting	None	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
(09.02.2017)			
Eleventh meeting (15.03.2017)	None	N/A	N/A
Twelfth meeting (19.04.2017)	None	N/A	N/A
Thirteenth meeting (25.05.2017)	None	N/A	N/A
Fourteenth meeting (26.05.2017)	None	N/A	N/A
Fifteenth meeting (22.06.2017)	Apologies received.	N/A	N/A
Sixteenth meeting (28.07.2017)	None	N/A	N/A
Seventeenth meeting (07.12.2017)			

13 **Beverley Hunt**

Committee meeting	Declaration of interest	Classification	Action taken
On application	Medical director and trustee of Thrombosis UK.	Personal non-financial specific	Declare and participate
First meeting (02.03.2016)	Thrombosis UK now accepts payment from pharmaceutical companies. BH has previously declared her involvement with Thrombosis UK.	Non-personal financial specific	Declare and participate
Second meeting (22.04.2016)	No change to existing declarations.	N/A	N/A
Third meeting (01.06.2016)	Apologies received.	N/A	N/A
Fourth meeting (20.07.2016)	Apologies received.	N/A	N/A
Fifth meeting (16.09.2016)	No change to existing declarations.	N/A	N/A
Sixth meeting (19.10.2016)	No change to existing declarations.	N/A	N/A
Seventh	Attended the All-party	Personal non-financial	Declare and participate

Committee meeting	Declaration of interest	Classification	Action taken
meeting (01.12.2016)	parliamentary thrombosis group (APPTG) round table.	specific	
Eight meeting (05.01.2017)	No change to existing declarations.	N/A	N/A
Ninth meeting (08.02.2017)	Principal Investigator for NIHR funded trial of stockings for VTE prophylaxis in surgical patients	Non-personal financial specific	Declare and participate
Tenth meeting (09.02.2017)	No change to existing declarations.	N/A	N/A
Eleventh meeting (15.03.2017)	Declared 20 recent articles 4 related to VTE prophylaxis. None applicable to topic under discussion: 1. Hunt BJ. The effect of BMI on haemostasis: Implications for thrombosis in women's health. Thrombosis Research. 2017; 151 Suppl 1:S53-s55 2. ISTH Steering Committee for World Thrombosis Day. Venous thromboembolism: A Call for risk assessment in all hospitalised patients. Thrombosis and Haemostasis. 2016; 116(5):777-779 3. Humes DJ, Walker AJ, Hunt BJ, Sultan AA, Ludvigsson JF, West J. Risk of symptomatic venous thromboembolism following emergency appendicectomy in adults. British Journal of Surgery. 2016; 103(4):443-450 4. Hunt BJ. Blood clots are more common (and deadly) than you may think. Huffington Post. 2016. Full text available from: http://www.huffingtonpost.co.uk/dr-beverley-hunt/blood-clots-are-more-comm_b_12466180.html	Personal non-financial non-specific	Declare and participate
Twelfth meeting (19.04.2017)	Apologies received.	N/A	N/A
Thirteenth	No change to existing	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
meeting (25.05.2017)	declarations.		
Fourteenth meeting (26.05.2017)	No change to existing declarations.	N/A	N/A
Fifteenth meeting (22.06.2017)	No change to existing declarations.	N/A	N/A
Sixteenth meeting (28.07.2017)	Chaired meeting Thrombosis TB.	Personal non-financial non-specific interest	Declare and participate
Seventeenth meeting (07.12.2017)			

14 **Josie Jenkinson (co-opted member)**

Committee meeting	Declaration of interest	Classification	Action taken
Ninth meeting (08.02.2017)	None	N/A	N/A

15 **Nicholas Levy (co-opted member)**

Committee meeting	Declaration of interest	Classification	Action taken
On application	None	N/A	N/A

16 **Donald McBride (orthopaedic subgroup member)**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (24.06.2016)	None	N/A	N/A
Second meeting (20.10.2016)	None	N/A	N/A
Third meeting (27.01.2017)	None	N/A	N/A
Fourth meeting (31.03.2017)	None	N/A	N/A
Fifth meeting (26.05.2017)	None	N/A	N/A
Sixth meeting (22.06.2017)	None	N/A	N/A

17 **Colin Nnadi (orthopaedic subgroup member)**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (24.06.2016)	None	N/A	N/A
Second meeting (20.10.2016)	None	N/A	N/A
Third meeting (27.01.2017)	None	N/A	N/A
Fourth meeting (31.03.2017)	None	N/A	N/A
Fifth meeting (26.05.2017)	None	N/A	N/A
Sixth meeting (22.06.2017)	None	N/A	N/A

18

19 **Simon Noble**

Committee meeting	Declaration of interest	Classification	Action taken
On application	Has given lectures for Leo Pharma and Pfizer in the past 12 months; no fee taken. Medical Director (Wales) for Thrombosis UK (formerly Lifeblood).	Non-personal non-financial specific Personal non-financial specific	Declare and participate Declare and participate
First meeting (02.03.2016)	Thrombosis UK now accepts payment from pharmaceutical companies. SN has previously declared his involvement with Thrombosis UK.	Non-personal financial specific	Declare and participate
Second meeting (22.04.2016)	No change to existing declarations	N/A	N/A
Third meeting (01.06.2016)	Apologies received	N/A	N/A
Fourth meeting (20.07.2016)	Apologies received	N/A	N/A
Fifth meeting (16.09.2016)	No change to existing declarations	N/A	N/A
Sixth	No change to existing	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
meeting (19.10.2016)	declarations		
Seventh meeting (01.12.2016)	No change to existing declarations	N/A	N/A
Eight meeting (05.01.2017)	No change to existing declarations	N/A	N/A
Ninth meeting (08.02.2017)	No change to existing declarations	N/A	N/A
Tenth meeting (09.02.2017)	No change to existing declarations	N/A	N/A
Eleventh meeting (15.03.2017)	Apologies received	N/A	N/A
Twelfth meeting (19.04.2017)	Apologies received	N/A	N/A
Thirteenth meeting (25.05.2017)	No change to existing declarations.	N/A	N/A
Fourteenth meeting (26.05.2017)	Apologies received.	N/A	N/A
Fifteenth meeting (22.06.2017)	Apologies received.	N/A	N/A
Sixteenth meeting (28.07.2017)	Apologies received.	N/A	N/A
Seventeenth meeting (07.12.2017)			

20 **Rachel Rayment (obstetric subgroup member)**

Committee meeting	Declaration of interest	Classification	Action taken
On application	Attendance at Bayer annual expert clotters meeting 2016 (travel, accommodation and food).	Personal, financial, specific	Declare and participate (relates to accepted expenses under DOI policy)
First meeting (14.03.2017)	Bayer annual expert clotters meeting 2017. CSL expenses for EAHAD 2017	Personal, financial, specific	Declare and participate (relates to accepted expenses under DOI policy)
Second meeting (24.05.2017)	No change to existing declarations.	N/A	N/A

21 **Mike Reed (orthopaedic subgroup member)**

Committee meeting	Declaration of interest	Classification	Action taken
On application	No links to manufacturers or bodies involved in VTE. Grants: Academic Health Science Network - NENC and Heraeus Medical - Spreading the use of high dose antibiotic cement to prevent infection following surgery for hip fracture (lead applicant) -£84,452 Stryker - A randomised multicentre trial of 964 patients comparing the Thompsons stem with the Exeter/unitrax for hemiarthroplasty (chief investigator) £313,003 with treatment costs Heraeus Medical GMBH - Investigation of NucB anti-biofilm role in joints (co-applicant) £84,000 Zimmer Educational fellowship grant £45,923 Convatec Clinical audit: £30,000 Speaker fees: Zimmer Biomet Heraeus	 Non-personal, financial, non-specific Non-personal, financial, non-specific Non-personal, financial, non-specific Non-personal, financial, non-specific Non-personal, financial, non-specific Personal, financial, non-specific Personal, financial, non-specific	 Declare and participate Declare and participate Declare and participate Declare and participate Declare and participate Declare and participate Declare and participate
First meeting (24.06.2016)	No change to existing declarations.	N/A	N/A
Second meeting (20.10.2016)	No change to existing declarations	N/A	N/A
Third meeting (27.01.2017)	No change to existing declarations	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
Fourth meeting (31.03.2017)	No changes to existing declarations	N/A	N/A
Fifth meeting (26.05.2017)	None	N/A	N/A
Sixth meeting (22.06.2017)	None	N/A	N/A

22 **Alexandra Rees**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (02.03.2016)	None	N/A	N/A
Second meeting (22.04.2016)	None	N/A	N/A
Third meeting (01.06.2016)	Apologies received	N/A	N/A
Fourth meeting (20.07.2016)	None	N/A	N/A
Fifth meeting (16.09.2016)	None	N/A	N/A
Sixth meeting (19.10.2016)	None	N/A	N/A
Seventh meeting (01.12.2016)	None	N/A	N/A
Eight meeting (05.01.2017)	None	N/A	N/A
Ninth meeting (08.02.2017)	None	N/A	N/A
Tenth meeting (09.02.2017)	None	N/A	N/A
Eleventh meeting (15.03.2017)	None	N/A	N/A
Twelfth meeting (19.04.2017)	None	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
Thirteenth meeting (25.05.2017)	None	N/A	N/A
Fourteenth meeting (26.05.2017)	Apologies received	N/A	N/A
Fifteenth meeting (22.06.2017)	None	N/A	N/A
Sixteenth meeting (28.07.2017)	None	N/A	N/A
Seventeenth meeting (07.12.2017)			

23 **Nigel Rossiter (orthopaedic subgroup member)**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (24.06.2016)	Director OrthoISIS Medical Indemnity Insurance Scheme (remunerated) Trustee Primary Trauma Care Foundation charity (not remunerated)	Personal financial non-specific Personal non-financial non-specific	Declare and participate Declare and participate
Second meeting (20.10.2016)	No change to existing declarations	N/A	N/A
Third meeting (27.01.2017)	No change to existing declarations	N/A	N/A
Fourth meeting (31.03.2017)	No change to existing declarations	N/A	N/A
Fifth meeting (26.05.2017)	None	N/A	N/A
Sixth meeting (22.06.2017)	None	N/A	N/A

24 **Karen Sheares**

Committee meeting	Declaration of interest	Classification	Action taken
On application	Received educational support (travel, accommodation and registration) from GSK to attend the European Respiratory Society Annual	Personal financial non-specific	Declare and participate

Committee meeting	Declaration of interest	Classification	Action taken
	Congress in September 2015.		
First meeting (02.03.2016)	No change to existing declarations	N/A	N/A
Second meeting (22.04.2016)	No change to existing declarations	N/A	N/A
Third meeting (01.06.2016)	Giving a VTE update lecture for the Royal College of Physicians in June 2016.	Personal non-financial specific	Declare and participate
Fourth meeting (20.07.2016)	No change to existing declarations	N/A	N/A
Fifth meeting (16.09.2016)	No change to existing declarations	N/A	N/A
Sixth meeting (19.10.2016)	Educational support to attend the Annual European respiratory Society International Conference from Actelion (paid for registration).	Personal financial non-specific	Declare and participate
Seventh meeting (01.12.2016)	No change to existing declarations	N/A	N/A
Eight meeting (05.01.2017)	No change to existing declarations	N/A	N/A
Ninth meeting (08.02.2017)	No change to existing declarations	N/A	N/A
Tenth meeting (09.02.2017)	No change to existing declarations	N/A	N/A
Eleventh meeting (15.03.2017)	No change to existing declarations	N/A	N/A
Twelfth meeting (19.04.2017)	Apologies received. Receiving educational support (registration, accommodation and travel) from Actelion to attend the American Thoracic Society Annual Congress in May 2017.	Reasonable travel expenses	Declare and participate
Thirteenth meeting (25.05.2017)	No new DOIs	N/A	N/A
Fourteenth meeting (26.05.2017)	No new DOIs	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
Fifteenth meeting (22.06.2017)	Apologies received	N/A	N/A
Sixteenth meeting (28.07.2017)	Apologies received	N/A	N/A
Seventeenth meeting (07.12.2017)			

25 **Kimberley Skinner (obstetric subgroup member)**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (14.03.2017)	None	N/A	N/A
Second meeting (24.05.2017)	None	N/A	N/A

26 **Gerard Stansby (Chair from September 2015-March 2017; Clinical Lead from April 2017)**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (02.03.2016)	None	N/A	N/A
Second meeting (22.04.2016)	None	N/A	N/A
Third meeting (01.06.2016)	None	N/A	N/A
Fourth meeting (20.07.2016)	None	N/A	N/A
Fifth meeting (16.09.2016)	None	N/A	N/A
Sixth meeting (19.10.2016)	None	N/A	N/A
Seventh meeting (01.12.2016)	None	N/A	N/A
Eight meeting (05.01.2017)	None	N/A	N/A
Ninth meeting	Author on two systematic reviews for VTE prophylaxis:	Personal non-financial specific	Declare and step down as Chair, participation as

Committee meeting	Declaration of interest	Classification	Action taken
(08.02.2017)	• thigh versus knee length stockings in postoperative surgical patients • Cochrane review of IPCD plus pharmacological prophylaxis in surgical, trauma or ICU patients		committee member thereafter
Tenth meeting (09.02.2017)	No change to existing declarations.	N/A	N/A
Eleventh meeting (15.03.2017)	Paper to be published for protocol relating to research, not any results. Graduated compression stockings as an adjunct to low dose low molecular weight heparin in venous thromboembolism prevention in surgery - a multi-centre randomised controlled trial [ISRCTN13911492] by Mr. Joseph Shalhoub,John Norrie; Christopher Baker; Andrew Bradbury; Karen Dhillon; Tamara Everington; Manj Gohel; Zaed Hamady; Francine Heatley; Jemma Hudson; Beverley J Hunt; Gerard Stansby; Annya Stephens-Boal; David Warwick; Alun H Davies is accepted by the European Journal of Vascular and Endovascular Surgery.	Personal non-financial specific	Declare and participate
Twelfth meeting (19.04.2017)	GAPS protocol (ISRCTN13911492) declared at last committee meeting for which Gerry is one of the authors has now been published.	Personal non-financial specific	Declare and participate
Thirteenth meeting (25.05.2017)	No change to existing declarations	N/A	N/A
Fourteenth meeting (26.05.2017)	No change to existing declarations	N/A	N/A
Fifteenth meeting (22.06.2017)	No change to existing declarations	N/A	N/A
Sixteenth meeting (28.07.2017)	No change to existing declarations		

Committee meeting	Declaration of interest	Classification	Action taken
Seventeenth meeting (07.12.2017)			

27 **Hazel Trender**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (02.03.2016)	None	N/A	N/A
Second meeting (22.04.2016)	None	N/A	N/A
Third meeting (01.06.2016)	None	N/A	N/A
Fourth meeting (20.07.2016)	Apologies received	N/A	N/A
Fifth meeting (16.09.2016)	None	N/A	N/A
Sixth meeting (19.10.2016)	None	N/A	N/A
Seventh meeting (01.12.2016)	None	N/A	N/A
Eight meeting (05.01.2017)	Sponsored by MEDI UK to attend the vascular Society annual conference in Manchester in November 2016. This included accommodation and registration. MEDI manufacture compression hosiery amongst other things.	Personal non-financial specific (usual expenses)	Declare and participate
Ninth meeting (08.02.2017)	No change to existing declarations	N/A	N/A
Tenth meeting (09.02.2017)	No change to existing declarations	N/A	N/A
Eleventh meeting (15.03.2017)	No change to existing declarations	N/A	N/A
Twelfth	No change to existing	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
meeting (19.04.2017)	declarations		
Thirteenth meeting (25.05.2017)	No change to existing declarations	N/A	N/A
Fourteenth meeting (26.05.2017)	Apologies received	N/A	N/A
Fifteenth meeting (22.06.2017)	No change to existing declarations	N/A	N/A
Sixteenth meeting (28.07.2017)	No change to existing declarations	N/A	N/A
Seventeenth meeting (07.12.2017)			

28 **Jen Watson**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (02.03.2016)	LEO Pharma has sponsored masterclasses at the Marsden hospital; no direct involvement in organizing these. Paid for article written in the Nursing Times on VTE and thrombosis.	Non-personal financial specific Personal financial specific	Declare and participate Declare and participate (Educational article. Nursing Times does not fund or gain from any product relating to VTE)
Second meeting (22.04.2016)	Approached by Anti-coagulation and Leo Pharma to work alongside them in raising awareness. Discussions are preliminary but may use the Leo Pharma Patient Education film as part of our patient and staff education amongst patients and staff.	Non-personal non-financial specific	Declare and participate
Third meeting (01.06.2016)	No change to existing declarations	N/A	N/A
Fourth meeting (20.07.2016)	No change to existing declarations	N/A	N/A
Fifth meeting (16.09.2016)	No change to existing declarations	N/A	N/A
Sixth	Attended the All-party	Personal non-financial	Declare and participate

Committee meeting	Declaration of interest	Classification	Action taken
meeting (19.10.2016)	parliamentary thrombosis group (APPTG) round table	specific	
Seventh meeting (01.12.2016)	No change to existing declarations	N/A	N/A
Eight meeting (05.01.2017)	No change to existing declarations	N/A	N/A
Ninth meeting (08.02.2017)	No change to existing declarations	N/A	N/A
Tenth meeting (09.02.2017)	No change to existing declarations	N/A	N/A
Eleventh meeting (15.03.2017)	No change to existing declarations	N/A	N/A
Twelfth meeting (19.04.2017)	Apologies received	N/A	N/A
Thirteenth meeting (25.05.2017)	No change to existing declarations	N/A	N/A
Fourteenth meeting (26.05.2017)	Apologies received	N/A	N/A
Fifteenth meeting (22.06.2017)	Apologies received	N/A	N/A
Sixteenth meeting (28.07.2017)	No change to existing declarations	N/A	N/A
Seventeenth meeting (07.12.2017)			

29

30 **Martin Yates**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting (02.03.2016)	None	N/A	N/A
Second meeting (22.04.2016)	Guest Speaker – VTE Patient Experience – Thrombosis UK. Travel expenses only. VTE Patient Experience Story –	Personal non-financial specific Personal non-financial	Declare and participate

Committee meeting	Declaration of interest	Classification	Action taken
	Hayward Medical Communications Volunteer - Patient Experience Panel – Papworth Hospital	specific Personal non-financial specific	
Third meeting (01.06.2016)	Apologies received	N/A	N/A
Fourth meeting (20.07.2016)	No change to existing declarations	N/A	N/A
Fifth meeting (16.09.2016)	No change to existing declarations	N/A	N/A
Sixth meeting (19.10.2016)	No change to existing declarations	N/A	N/A
Seventh meeting (01.12.2016)	No change to existing declarations	N/A	N/A
Eight meeting (05.01.2017)	No change to existing declarations	N/A	N/A
Ninth meeting (08.02.2017)	No change to existing declarations	N/A	N/A
Tenth meeting (09.02.2017)	No change to existing declarations	N/A	N/A
Eleventh meeting (15.03.2017)	No change to existing declarations	N/A	N/A
Twelfth meeting (19.04.2017)	No change to existing declarations	N/A	N/A
Thirteenth meeting (25.05.2017)	I have been invited to review a research funding application for the National Institute for Health Research Central Commissioning Facility:-The Research for Patient Benefit (RfPB) Programme Research Title: Advanced Resuscitation Room Monitoring Study (ARMS): Randomised controlled trial to test the feasibility of comparing combined advanced minimally-invasive patient monitoring in the	Personal financial non-specific	Declare and participate

Committee meeting	Declaration of interest	Classification	Action taken
	emergency department versus standard care. The RfPB programme offers reimbursement for the time and effort involved in commenting on funding applications in accordance with the Guide for CCF public contributors about the payment of fees and expenses.		
Fourteenth meeting (26.05.2017)	No changes to existing declarations.	N/A	N/A
Fifteenth meeting (22.06.2017)	I have been invited to review a research funding application for the National Institute for Health Research Central Commissioning Facility:-The Research for Patient Benefit (RfPB) Programme Research Title: Advanced Resuscitation Room Monitoring Study (ARMS): Randomised controlled trial to test the feasibility of comparing combined advanced minimally-invasive patient monitoring in the emergency department versus standard care. The RfPB programme offers reimbursement for the time and effort involved in commenting on funding applications in accordance with the Guide for CCF public contributors about the payment of fees and expenses.	Personal financial non-specific	Declare and participate
Sixteenth meeting (28.07.2017)	No change to existing declarations	N/A	N/A
Seventeenth meeting (07.12.2017)			

31

32 **NGC team**

Committee meeting	Declaration of interest	Classification	Action taken
First meeting	In receipt of NICE commissions	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
(02.03.2016)			
Second meeting (22.04.2016)	No change to existing declarations	N/A	N/A
Third meeting (01.06.2016)	No change to existing declarations	N/A	N/A
Fourth meeting (20.07.2016)	No change to existing declarations	N/A	N/A
Fifth meeting (16.09.2016)	No change to existing declarations	N/A	N/A
Sixth meeting (19.10.2016)	No change to existing declarations	N/A	N/A
Seventh meeting (01.12.2016)	No change to existing declarations	N/A	N/A
Eight meeting (05.01.2017)	No change to existing declarations	N/A	N/A
Ninth meeting (08.02.2017)	No change to existing declarations	N/A	N/A
Tenth meeting (09.02.2017)	No change to existing declarations	N/A	N/A
Eleventh meeting (15.03.2017)	No change to existing declarations	N/A	N/A
Twelfth meeting (19.04.2017)	No change to existing declarations	N/A	N/A
Thirteenth meeting (25.05.2017)	No change to existing declarations	N/A	N/A
Fourteenth meeting (26.05.2017)	No change to existing declarations	N/A	N/A
Fifteenth meeting (22.06.2017)	No change to existing declarations	N/A	N/A
Sixteenth meeting (28.07.2017)	No change to existing declarations	N/A	N/A
Seventeenth meeting	No change to existing declarations	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
(07.12.2017)			

33 **NIHR team**

Committee meeting	Declaration of interest	Classification	Action taken
Nicholas Hicks (10.07.2017)	None	N/A	N/A

34

35

Appendix C: Clinical review protocols

C.1 Risk assessment for people admitted to hospital

C.1.1 Patients admitted to hospital

Table 1: Review protocol: What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE in a patient who is admitted to hospital?

Review question	What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE in a patient who is admitted to hospital?
Objective	To evaluate which risk tool can best identify those people at risk of VTE, in order to identify people who will need prophylaxis
Population	Adults and young people (aged 16 or over) admitted to hospital
Risk tools	Derived and validated risk tools identified in literature
Target condition(s)	• VTE (symptomatic or asymptomatic) (up to 90 days): DVT and PE • VTE-related mortality (up to 90 days): DVT/PE related morality confirmed by: CT scan; pulmonary angiogram; ventilation/ perfusion scan; spiral CT scan; autopsy; echocardiography ; clinical examination with the presence of proven VTE. Diagnosis should not be based on Chest X-rays or clinical examination alone. • DVT alone (up to 90 days): DVT confirmed by: radioiodine fibrinogen uptake test; venography; duplex (Doppler) ultrasound; MRI; impedance Plethysmography (used as rule out tool). Diagnosis should not be based on d-dimer assay test or clinical examination alone. • PE alone (up to 90 days): PE confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical examination with the presence of proven VTE. Diagnosis should not be based on Chest X-rays or clinical examination alone.
Exclusions	• Children and young people (<16 years) • Pregnant women • Tools not externally validated or not validated by split half validation • Derivation studies
Search strategy	Databases: Medline, Embase, the Cochrane Library Dates/cut-offs: None
The review strategy	Prospective and retrospective cohort, externally validated or internally validated by split half validation
Analysis	Analysis: the ability of risk tool to predict each of the target conditions will be analysed separately Appraisal of methodological quality: methodological quality of each risk tool will be assessed using PROBAST Indirectness: risk tools will be downgraded for indirectness if definition of target conditions varies from definitions of above

C.1.2 Hospital admissions

Table 2: Review protocol: What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of major bleeding or the risk of bleeding in a patient who is admitted to hospital?

Review question	What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of major bleeding or the risk of bleeding in a patient who is admitted to hospital?
Objective	To evaluate which risk tool can best identify those people at risk of bleeding in order to identify those patients who will need prophylaxis
Population	Adults and young people (aged 16 or over) admitted to hospital
Risk tools	Derived and (externally or temporally) validated risk tools identified in literature
Target condition(s)	Major bleeding (up to 90 days). A major bleeding event meets one or more of the following criteria: • results in death • occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal) • results in the need for a transfusion of at least 2 units of blood • leads to a drop in haemoglobin of ≥2g/dl • a serious or life threatening clinical event • a surgical or medical intervention.
Exclusions	• Children and young people (<16 years) • Pregnant women • Tools not externally or temporally validated • Derivation studies
Search strategy	Databases: Medline, Embase, the Cochrane Library Dates/cut-offs: None
The review strategy	Prospective and retrospective cohort, externally validated or internally validated by split half validation
Analysis	Inclusion will be limited to papers which predict major bleeding associated with VTE. If no tools are identified the inclusion of tools to predict bleeding in similar populations (for example HAS-BLED score used for atrial fibrillation) will be considered. Appraisal of methodological quality: methodological quality of each risk tool will be assessed using PROBAST Indirectness: risk tools will be downgraded for indirectness if definition of target conditions varies from definitions of above

C.1.3 Risk assessment tools in patients admitted to hospital

Table 3: Review protocol: Reducing the rate of VTE in patients who are admitted to hospital

Review question	**How clinically and cost effective are risk assessment tools at reducing the rate of VTE in patients who are admitted to hospital?**
Review population	Adults (aged 16 or over) admitted to hospital
Interventions and comparisons	Intervention: Derived and validated risk tool for predicting the risk of VTE/DVT/PE/major bleeding The Department of Health risk tool (not validated) Comparisons: No risk tool, other risk tools
Outcomes	Critical: All-cause mortality (up to 90 days from hospital discharge)

Review question	How clinically and cost effective are risk assessment tools at reducing the rate of VTE in patients who are admitted to hospital?
	VTE (symptomatic or asymptomatic) (up to 90 days from hospital discharge) DVT (symptomatic or asymptomatic) (up to 90 days from hospital discharge) Pulmonary embolism (up to 90 days from hospital discharge) Fatal pulmonary embolism (up to 90 days from hospital discharge) Major bleeding (up to 90 days from hospital discharge) Quality of life (validated scores) (up to 90 days from hospital discharge) Important: Fatal bleeding (up to 90 days from hospital discharge) Clinically relevant non-major bleeding (up to 45 days from hospital discharge) Heparin-induced thrombocytopenia (up to 90 days from hospital discharge) Hospital length of stay (up to 90 days from hospital discharge) Unplanned readmission (up to 90 days from hospital discharge) Haemorrhagic stroke (up to 90 days from hospital discharge)
Study design	Systematic reviews of RCTs or RCTs. If no RCTs are identified, observational studies (including before and after studies) will be considered
Crossover study	Not permitted
Duration of study	Minimum: 7 days Maximum: 90 days
Sensitivity/other analysis	If studies have pre-specified in their protocols that results for any of these subgroup populations will be analysed separately, then they will be included in the subgroup analysis.
Subgroup analyses if there is heterogeneity	Strata: Target condition (VTE/PE/DVT/major bleeding) Medical/surgery Type of surgery Cancer Subgroup: none
Search criteria	Databases: Medline, Embase, the Cochrane Library Date limits for search: None Language: English only

C.2 Risk assessment for people having day procedures

C.2.1 VTE day procedures

Table 4: Review protocol: What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE in patients who are having day procedures (including surgery and chemotherapy) at hospital?

Review question	What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE in patients who are having day procedures (including surgery and chemotherapy) at hospital?
Objective	To evaluate which risk tool can best identify those people at risk of VTE, in order to identify people who will need prophylaxis
Population	Adults and young people (aged 16 or over) who are having day procedures (including

	surgery and chemotherapy
Risk tools	Derived and validated risk tools identified in literature
Target condition(s)	• VTE (symptomatic or asymptomatic) (7- 90 days; up to 180 days for people having cancer treatment): DVT and PE • VTE-related mortality (7-90 days; up to 180 days for people having cancer treatment): DVT/PE related morality confirmed by: CT scan; pulmonary angiogram; ventilation/ perfusion scan; spiral CT scan; autopsy; echocardiography ; clinical examination with the presence of proven VTE. Diagnosis should not be based on Chest X-rays or clinical examination alone. • DVT alone (7-90 days; up to 180 days for people having cancer treatment): DVT confirmed by: radioiodine fibrinogen uptake test; venography; duplex (Doppler) ultrasound; MRI; impedance Plethysmography (used as rule out tool). Diagnosis should not be based on d-dimer assay test or clinical examination alone. • PE alone (7- 90 days; up to 180 days for people having cancer treatment): PE confirmed by: CT scan; pulmonary angiogram; ventilation/ perfusion scan; spiral CT scan; autopsy; echocardiography ; clinical examination with the presence of proven VTE. Diagnosis should not be based on Chest X-rays or clinical examination alone.
Exclusions	• Children and young people (<16 years) • Pregnant women • Tools not externally validated or not validated by split half validation • Derivation studies
Search strategy	Databases: Medline, Embase, the Cochrane Library Dates/cut-offs: None
The review strategy	Prospective and retrospective cohort, externally validated or internally validated by split half validation
Analysis	Analysis: the ability of risk tool to predict each of the target conditions will be analysed separately Appraisal of methodological quality: methodological quality of each risk tool will be assessed using PROBAST Indirectness: risk tools will be downgraded for indirectness if definition of target conditions varies from definitions of above

C.2.2 Major bleeding day procedures

Table 5: Review protocol: What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of major bleeding or the risk of bleeding in patients who are having day procedures (including surgery and chemotherapy) at hospital?

Review question	What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of major bleeding or the risk of bleeding in patients who are having day procedures (including surgery and chemotherapy) at hospital?
Objective	To evaluate which risk tool can best identify those people at risk of bleeding in order to identify those patients who will need prophylaxis
Population	Adults (aged 16 or over) who are having day procedures (including surgery and chemotherapy)
Risk tools	Derived and validated risk tools identified in literature
Target condition(s)	Major bleeding (up to 90 days). A major bleeding event meets one or more of the following criteria: • results in death • occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal)

	• results in the need for a transfusion of at least 2 units of blood • leads to a drop in haemoglobin of ≥2g/dl • a serious or life threatening clinical event a surgical or medical intervention.
Exclusions	• Children and young people (<16 years) • Pregnant women • Tools not externally validated or not validated by split half validation • Derivation studies
Search strategy	Databases: Medline, Embase, the Cochrane Library Dates/cut-offs: None
The review strategy	Prospective and retrospective cohort, externally validated or internally validated by split half validation
Analysis	Inclusion will be limited to papers which predict major bleeding associated with VTE. If no tools are identified the inclusion of tools to predict bleeding in similar populations (for example HAS-BLED score used for atrial fibrillation) will be considered. Appraisal of methodological quality: methodological quality of each risk tool will be assessed using PROBAST Indirectness: risk tools will be downgraded for indirectness if definition of target conditions varies from definitions of above

C.2.3 Risk assessment tools in patients who are having day procedures (including surgery and chemotherapy) at hospital

Table 6: Review protocol: Reducing the rate of VTE in patients who are having day procedures (including surgery and chemotherapy)

Review question	How clinically and cost effective are risk assessment tools at reducing the rates of VTE in patients who are having day procedures (including surgery and chemotherapy) at hospital?
Review population	Adults (aged 16 or over) who are having day procedures (including surgery and chemotherapy)
Interventions and comparisons	Intervention: Derived and validated risk tool for predicting the risk of VTE/DVT/PE/major bleeding The Department of Health risk tool (not validated) Comparisons: No risk tool, other risk tools
Outcomes	Critical: All-cause mortality (up to 90 days from hospital discharge) VTE (symptomatic or asymptomatic) (7- 90 days from hospital discharge) DVT (symptomatic or asymptomatic) (7- 90 days from hospital discharge) Pulmonary embolism (7- 90 days from hospital discharge) Fatal pulmonary embolism (up to 90 days from hospital discharge) Major bleeding (up to 90 days from hospital discharge) Quality of life (validated scores) (up to 90 days from hospital discharge) Important: Fatal bleeding (up to 90 days from hospital discharge) Clinically relevant non-major bleeding (up to 45 days from hospital discharge) Heparin-induced thrombocytopenia (up to 90 days from hospital discharge) Hospital length of stay (up to 90 days from hospital discharge)

Review question	How clinically and cost effective are risk assessment tools at reducing the rates of VTE in patients who are having day procedures (including surgery and chemotherapy) at hospital?
	Unplanned readmission (up to 90 days from hospital discharge) Haemorrhagic stroke (up to 90 days from hospital discharge)
Study design	Systematic reviews of RCTs or RCTs. If no RCTs are identified, consider observational studies (including before and after studies)
Crossover study	Not permitted
Duration of study	Minimum: 7 days Maximum: 90 days
Sensitivity/other analysis	If studies have pre-specified in their protocols that results for any of these subgroup populations will be analysed separately, then they will be included in the subgroup analysis.
Subgroup analyses if there is heterogeneity	Strata: Target condition Medical/surgery Type of surgery Cancer
Search criteria	Databases: Medline, Embase, the Cochrane Library Date limits for search: None Language: English only

C.3 Reassessment

C.3.1 Reassessment of people who are admitted to hospital

Table 7: Review protocol: Reassessment of the risk of VTE of people who are admitted to hospital

Review question	How effective is reassessment of the risk of VTE of people who are admitted to hospital?
Review population	Adults (aged 16 or over) admitted to hospital
Interventions and comparisons	Intervention: Tools identified in intervention risk assessment reviews only: derived and (temporally or externally) validated risk tool reassessment for predicting the risk of VTE/DVT/PE/major bleeding; Department of Health risk tool (not validated) Comparisons: No risk tool, other risk tools, first assessment
Outcomes	Critical: All-cause mortality (duration of study) VTE (symptomatic or asymptomatic) (duration of study) DVT (symptomatic or asymptomatic) (duration of study) Pulmonary embolism (duration of study) Fatal pulmonary embolism (duration of study) Major bleeding (duration of study) Quality of life (validated scores) (duration of study) Important: Fatal bleeding (duration of study) Heparin-induced thrombocytopenia (duration of study) Clinically relevant non-major bleeding (duration of study)

Review question	How effective is reassessment of the risk of VTE of people who are admitted to hospital?
	Hospital length of stay (duration of study) Unplanned readmission (duration of study) Haemorrhagic stroke (duration of study)
Study design	Systematic reviews of RCTs or RCTs. If no RCTs are identified, consider observational studies (including before and after studies)
Crossover study	Not permitted
Duration of study	Minimum: 7 days Maximum: 90 days
Sensitivity/other analysis	If studies have pre-specified in their protocols that results for any of these subgroup populations will be analysed separately, then they will be included in the subgroup analysis.
Subgroup analyses if there is heterogeneity	Strata: Target condition Medical/surgery Type of surgery Cancer
Search criteria	Databases: Medline, Embase, the Cochrane Library Date limits for search: None Language: English only

C.3.2 Reassessment of people who are having day procedures at hospital

Table 8: Review protocol: Reassessment of the risk of VTE of people who are having day procedures at hospital

Review question	How effective is reassessment of the risk of VTE of people who are having day procedures at hospital?
Review population	Adults (aged 16 or over) who are having day procedures (including surgery and chemotherapy)
Interventions and comparisons	Intervention: Tools identified in intervention risk assessment reviews only: derived and (temporally or externally) validated risk tool reassessment for predicting the risk of VTE/DVT/PE/major bleeding; Department of Health risk tool (not validated) Comparisons: No risk tool, other risk tools, first assessment
Outcomes	Critical: All-cause mortality (duration of study) VTE (symptomatic or asymptomatic) (duration of study) DVT (symptomatic or asymptomatic) (duration of study) Pulmonary embolism (duration of study) Fatal pulmonary embolism (duration of study) Major bleeding (duration of study) Quality of life (validated scores) (duration of study) Important: Fatal bleeding (duration of study) Heparin-induced thrombocytopenia (duration of study) Clinically relevant non-major bleeding (duration of study) Hospital length of stay (duration of study)

Review question	How effective is reassessment of the risk of VTE of people who are having day procedures at hospital?
	Unplanned readmission (duration of study) Haemorrhagic stroke (duration of study)
Study design	Systematic reviews of RCTs or RCTs. If no RCTs are identified, consider observational studies (including before and after studies)
Crossover study	Not permitted
Duration of study	Minimum: 7 days Maximum: 90 days
Sensitivity/other analysis	If studies have pre-specified in their protocols that results for any of these subgroup populations will be analysed separately, then they will be included in the subgroup analysis.
Subgroup analyses if there is heterogeneity	Strata: Target condition Medical/surgery Type of surgery Cancer
Search criteria	Databases: Medline, Embase, the Cochrane Library Date limits for search: None Language: English only

C.4 Risk assessment for pregnant women and women up to 6 weeks postpartum

Table 9: Review protocol: Prognostic accuracy of risk tools for VTE in pregnant women

Review question	What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE in pregnant women who are admitted to hospital and midwife units including up to 6 weeks after giving birth?
Objective	To evaluate which risk tool can best identify those people at risk of VTE, in order to identify those patients who will need prophylaxis
Population	Pregnant women who are admitted to hospital and midwife units including up to 6 weeks after giving birth.
Risk tool	Derived and validated risk tools identified in literature
Target condition(s)	• VTE (symptomatic or asymptomatic) (up to 90 days) • VTE-related mortality (up to 90 days) • DVT alone (up to 90 days) • PE alone (up to 90 days)
Statistical outcomes	Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values) (define thresholds) • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) • Reclassification • Other statistical measures: for example, D statistic, R^2 statistic and Brier score
Study types	Prospective and retrospective cohort, externally validated or internally validated by split half validation
Exclusions	Tools not externally validated or not validated by split half validation

Review question	What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE in pregnant women who are admitted to hospital and midwife units including up to 6 weeks after giving birth?
Search study	Databases: Medline, Embase, the Cochrane Library Dates/cut-offs: None
The review strategy	Appraisal of methodological quality: methodological quality of each risk tool will be assessed using PROBAST Indirectness: risk tools will be downgraded for indirectness if definition of target conditions varies from definitions above

Table 10: Review protocol: Prognostic accuracy of risk tools for major bleeding in pregnant women

Review question	What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of major bleeding or the risk of bleeding in pregnant women who are admitted to hospital and midwife units including up to 6 weeks after giving birth?
Objective	To evaluate which risk tool can best identify those people at risk of bleeding in order to identify those patients who will need prophylaxis
Population	Adults (aged 16 or over) who are having day procedures (including surgery and chemotherapy)
Risk tools	Derived and validated risk tools identified in literature
Target condition(s)	Major bleeding (up to 90 days). A major bleeding event meets one or more of the following criteria: • results in death • occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal) • results in the need for a transfusion of at least 2 units of blood • leads to a drop in haemoglobin of ≥2g/dl • a serious or life threatening clinical event a surgical or medical intervention.
Exclusions	• Children and young people (<16 years) • Pregnant women • Tools not externally validated or not validated by split half validation • Derivation studies
Search strategy	Databases: Medline, Embase, the Cochrane Library Dates/cut-offs: None
The review strategy	Prospective and retrospective cohort, externally validated or internally validated by split half validation
Analysis	Inclusion will be limited to papers which predict major bleeding associated with VTE. If no tools are identified the inclusion of tools to predict bleeding in similar populations (for example HAS-BLED score used for atrial fibrillation) will be considered. Appraisal of methodological quality: methodological quality of each risk tool will be assessed using PROBAST Indirectness: risk tools will be downgraded for indirectness if definition of target conditions varies from definitions of above

Table 11: Review protocol: Clinical and cost-effectiveness of risk tools in pregnant women

Review question	What is the clinical and cost-effectiveness of risk assessment tools, when each tool is followed by the appropriate treatment, at reducing the rates of VTE and/or bleeding in pregnant women who are admitted to hospital or midwife units?

Objectives	To evaluate the clinical effectiveness of different tools to predict the risk of VTE and/or major bleeding, when followed by appropriate treatment
Population and target condition	Pregnant women (including up to 6 weeks after giving birth) who are: • Admitted to hospital for 24 hours or more • Having day procedures including early pregnancy loss (miscarriage and termination) Target condition: VTE/DVT/PE/major bleeding
Prognostic test	Any structured risk assessment for predicting the risk of VTE/DVT/PE/major bleeding in pregnancy and postpartum women
Comparator	No risk assessment Different structured risk assessment tools compared to each other
Outcomes	Critical: • All-cause mortality (up to 90 days from hospital discharge) • VTE (symptomatic or asymptomatic) (inpatient to 90 days from hospital discharge) • DVT (symptomatic or asymptomatic) (inpatient to 90 days from hospital discharge) • Pulmonary embolism (inpatient to 90 days from hospital discharge) • Fatal pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 90 days from hospital discharge) • Quality of life (validated scores) (up to 90 days from hospital discharge) Important: • Fatal bleeding (up to 90 days from hospital discharge) • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • Hospital length of stay (up to 90 days from hospital discharge) • Unplanned readmission (up to 90 days from hospital discharge) • Haemorrhagic stroke (up to 90 days from hospital discharge)
Study design	Systematic reviews of RCTs or RCTs. If no RCTs then observational cohort data.
Search strategy	Databases: Medline, Embase, the Cochrane Library Date limits for search: None Language: English only
Duration of study	Minimum: 7 days follow-up Maximum: 150 days
Review strategy	Strata: • Target condition (VTE/PE/DVT/major bleeding)
Subgroup analyses if there is heterogeneity	Medical vs. surgical Pre- vs. post-natal

Table 12: Review protocol: Risk tools for reassessment for VTE and/or bleeding in pregnant women

Review question	How effective is reassessment of the risk of VTE and/or bleeding of pregnant women who are admitted to hospital or midwife units?
Objectives	To evaluate the effectiveness of reassessing the risk of VTE and/or bleeding of pregnant women who are admitted to hospital or midwife units. Reassessment may include booking, admission, admission for delivery, post-delivery assessment, re-admission post-delivery.

Population and target condition	Pregnant women (including up to 6 weeks after giving birth) who are: • Admitted to hospital for 24 hours or more • Having day procedures including early pregnancy loss (miscarriage and termination) Target condition: VTE/DVT/PE/major bleeding
Prognostic test	Any structured risk assessment for predicting the risk of VTE/DVT/PE/major bleeding in pregnancy and postpartum women
Comparator	No risk tool, other risk tools, first assessment
Outcomes	Critical: • All-cause mortality (duration of study) • VTE (symptomatic or asymptomatic) (duration of study) • DVT (symptomatic or asymptomatic) (duration of study) • Pulmonary embolism (duration of study) • Fatal pulmonary embolism (duration of study) • Major bleeding (duration of study) • Quality of life (validated scores) (duration of study) Important: • Fatal bleeding (duration of study) • Clinically relevant non-major bleeding (duration of study) • Hospital length of stay (duration of study) • Unplanned readmission (duration of study) • Haemorrhagic stroke (duration of study)
Study design	Systematic reviews of RCTs or RCTs. If no RCT's identified then observational cohort data.
Search strategy	Databases: Medline, Embase, the Cochrane Library Date limits for search: None Language: English only
Review strategy	Strata: • Target condition (VTE/PE/DVT/major bleeding)
Subgroup analyses if there is heterogeneity	Medical vs. surgical Pre- vs. post-natal

C.5 Giving information to patients and planning for discharge

Table 13: Review protocol: What information about VTE and VTE prophylaxis should be given to people who are admitted to hospital, having day procedures or outpatients post-discharge, and their family or carers?

Component	Description
Review question	What information about VTE and VTE prophylaxis should be given to people who are admitted to hospital, having day procedures or outpatients post-discharge, and their family or carers?
Objective	To identify the information about VTE and VTE prophylaxis that people who are admitted to hospital, having day procedures or outpatients post-discharge, and their family or carers want.
Population and setting	Adults and young people (16 years and older) who are: • Admitted to hospital

Component	Description
	• Having day procedures • Outpatients post-discharge who require information about VTE and VTE prophylaxis, and their family and carers Setting: • Primary and community care when continuing prophylaxis after hospital discharge • Secondary care
Context	Examples of possible themes • Standardised vs. conflicting information • Lack of information • Too much information • Types of information • When information is given • Informed consent for VTE prophylaxis • Who information is given to e.g. patient, family/carer • Who is giving information
Exclusions	• Community settings and hospices, except when continuing prophylaxis that has been started in hospital • Non-English studies
Search strategy	Databases: The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only. Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

Review strategy	**Study designs to be considered:**
	• Qualitative studies (for example, interviews, focus groups, observations)
	• Systematic review of qualitative studies
	Review strategy:
	• Population size and directness:
	  ○ No minimum sample size
	  ○ Studies with indirect populations will not be considered
	Appraisal of methodological quality
	The methodological quality of each study will be assessed using NGC modified NICE checklists and the quality of the body of evidence as a whole will be assessed by a GRADE CerQual approach for each review finding.
	Data synthesis
	Synthesis of qualitative research: thematic analysis – information synthesised into main review findings. Results presented in a detailed narrative and in table format with summary statements of main review findings.

C.6 General VTE prevention for everyone in hospital

None

C.7 Nursing care: Early mobilisation and hydration

None

C.8 Obesity

Table 14: Review protocol: What is the effectiveness of weight based dose-adjustment strategies of LMWH compared to fixed dose strategies of LMWH for people who are obese?

Review question	What is the effectiveness of weight based dose-adjustment strategies of LMWH compared to fixed dose strategies of LMWH for people who are obese?
Objectives	To find the most effective strategy for preventing VTE in people who are obese
Population	Adults and young people (16 years and older) who are obese (BMI > 30) and who are: • Admitted to hospital • Having day procedures • Outpatients post-discharge

Interventions	Pharmacological (fixed dose or weight adjusted dose):
	• Low molecular weight heparin (LMWH), licensed in UK:
	  ○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*)
	  ○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*)
	  ○ tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*)
	• LMWH, licensed in countries other than UK:
	  ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)
	  ○ Certoparin (3000 units daily)
	  ○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)
	  ○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)
	  ○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)
	*off-label

Comparisons	Fixed dose Weight adjusted dose
Outcomes	Critical outcomes: • All-cause mortality (up to 90 days from hospital discharge) • Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) • Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE • Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in

Review question	What is the effectiveness of weight based dose-adjustment strategies of LMWH compared to fixed dose strategies of LMWH for people who are obese?
	haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding • Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. • Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	People who are contraindicated for both mechanical and pharmacological prophylaxis Community settings and hospices, except when continuing prophylaxis that has been started in hospital People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: • LMWH Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated for pharmacological prophylaxis People who are contraindicated for mechanical prophylaxis
Subgroup analyses if there is heterogeneity	BMI: obese (obesity I and II, 30–34.9 kg/m^2); severely obese (obesity III, ≥40 kg/m^2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30)
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.9 People using antiplatelets

Table 15: Review protocol: People using anti-platelet agents at time of presentation

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people using antiplatelets agents at time of presentation?
Objectives	To find the most effective strategy for preventing VTE in people using antiplatelets (for example for people with chronic cardiovascular disease) on presentation to hospital?
Population	Adults and young people (16 years and older) in people using antiplatelet agents on presentation to hospital
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Vena caval filters Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people using antiplatelets agents at time of presentation?
Comparisons	Continuing/stopping antiplatelets (including single and dual agents) plus VTE prophylaxis treatment, versus continuing/stopping antiplatelets, plus one of the following: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge) (NMA outcome). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	People using antiplatelets for acute coronary syndromes (included in separate review) Community settings and hospices, except when continuing prophylaxis that has been started in hospital People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people using antiplatelets agents at time of presentation?
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Antiplatelet treatment
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness.
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.10 People using anticoagulation therapy

Table 16: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people having to interrupt anticoagulation therapy?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people having to interrupt anticoagulation therapy?
Objectives	To find the most effective strategy, including bridging therapy (stopping warfarin and replacing with pharmacological therapy), for preventing VTE in people having to interrupt anticoagulation therapy (for example warfarin)
Population	Adults and young people (16 years and older) having to interrupt anticoagulation therapy who are : Admitted to hospital Having day procedures Discharged from hospital Outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people having to interrupt anticoagulation therapy?
	Vena caval filters Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label
Comparisons	Continuing/stopping anticoagulants plus VTE prophylaxis treatment versus continuing/stopping anticoagulants, plus one of the following: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool)

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people having to interrupt anticoagulation therapy?
	Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study) Haemorrhagic stroke (up to 45 days from hospital discharge) Embolic stroke (up to 45 days from hospital discharge)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Community settings and hospices, except when continuing prophylaxis that has been started in hospital People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Medical/surgical Atrial fibrillation Mechanical heart valves
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people having to interrupt anticoagulation therapy?
	confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.11 Acute coronary syndromes

Table 17: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people being treated for acute coronary syndromes (using anticoagulants and/or anti-platelets)?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people being treated for acute coronary syndromes (using anticoagulants and/or anti-platelets)?
Objectives	To find the most effective strategy for preventing VTE in people being treated for acute coronary syndromes who are already being treated with anticoagulants and/or anti-platelets
Population	Adults and young people (16 years and older) being treated for acute coronary syndromes with anticoagulants and/or anti-platelets who are: Admitted to hospital Having day procedures Discharged from hospital Outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Vena caval filters Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK:

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people being treated for acute coronary syndromes (using anticoagulants and/or anti-platelets)?
	Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label
Comparisons	Treatment for acute coronary syndrome (anti-platelets; anticoagulants; anti-platelets and anticoagulants) plus VTE prophylaxis treatment, versus treatment for acute coronary syndromes plus one of the following: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge) (NMA outcome). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people being treated for acute coronary syndromes (using anticoagulants and/or anti-platelets)?
	Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Community settings and hospices, except when continuing prophylaxis that has been started in hospital People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Treatment for acute coronary syndrome
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.12 Acute stroke patients

Table 18: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are admitted to hospital with a stroke or who have a stroke in hospital?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are admitted to hospital with a stroke or who have a stroke in hospital
Objectives	To find the most effective strategy for preventing VTE in people who are admitted to hospital with a stroke or who have a stroke in hospital
Population	Adults and young people (16 years and older) who are admitted to hospital with a stroke or who have a stroke in hospital
Interventions	Mechanical: Anti-embolism stockings (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Vena caval filters Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are admitted to hospital with a stroke or who have a stroke in hospital
Comparisons	Treatment for stroke (anti-platelets/warfarin) plus VTE prophylaxis treatment, versus treatment for stroke (anti-platelets/warfarin), plus one of the following: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge) (NMA outcome). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study) Haemorrhagic transformation (for people without haemorrhagic stroke only) (up to 45 days from hospital discharge)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Community settings and hospices, except when continuing prophylaxis that has been started in hospital People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are admitted to hospital with a stroke or who have a stroke in hospital
	Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Type of stroke: ischemic; haemorrhagic; embolic
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.13 Acutely ill medical patients

Table 17: Review protocol: Acutely ill medical patients admitted to hospital

Review question	What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for acutely ill medical patients admitted to hospital?
Guideline condition and its definition	VTE prophylaxis. Definition: Prevention of VTE (DVT and PE) in hospital patients
Review population	Adults and young people (16 years and older) who are acutely ill medical patients admitted to hospital
	Adults Young people (aged 16 years or over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each	Anti-embolism stockings; Above knee Anti-embolism stockings; Below knee Anti-embolism stockings; Mixed above/below knee Intermittent pneumatic compression devices ; Full leg Intermittent pneumatic compression devices ; Below knee Intermittent pneumatic compression devices ; Mixed full leg/below knee Foot pumps or foot impulse devices ; Foot pumps

Review question	What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for acutely ill medical patients admitted to hospital?
other, unless otherwise stated)	Foot pumps or foot impulse devices ; Foot impulse Electrical stimulation Continuous passive motion Vena cava filters Unfractionated heparin ; Unfractionated heparin (low dose, administered subcutaneously) Low molecular weight heparin (licensed in UK); Dalteparin (1,250 units once daily - 5,000 units twice daily) Low molecular weight heparin (licensed in UK); Tinzaparin (2,500 units once daily – 9,000 units once daily) Low molecular weight heparin (licensed in UK); Enoxaparin (20mg once daily – 60mg twice daily) Vitamin K antagonists ; Warfarin (all doses) Vitamin K antagonists ; Acenocoumarol (all doses) Vitamin K antagonists ; Phenindione (all doses) Fondaparinux; Fondaparinux (all doses) Apixaban; Apixaban (all doses) Dabigatran; Dabigatran (all doses) Rivaroxaban; Rivaroxaban (all doses) Aspirin; Aspirin (up to 300mg) No treatment; Usual care No treatment; Placebo Low molecular weight heparin (not licensed in UK); bemiparin (2500 units once daily - 3500 units once daily) Low molecular weight heparin (not licensed in UK); certoparin (3000 units once daily) Low molecular weight heparin (not licensed in UK); nadroparin (2850 units once daily - up to 57 units/kg once daily) Low molecular weight heparin (not licensed in UK); parnaparin (3200 units once daily - 4250 units once daily) Low molecular weight heparin (not licensed in UK); reviparin (1750 units once daily - 4200 units once daily)
Outcomes	- All-cause mortality at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge. Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) (Dichotomous) CRITICAL - Pulmonary embolism) at 7-90 days from hospital discharge. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE (Dichotomous) CRITICAL - Major bleeding at up to 45 days from hospital discharge. A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (Dichotomous) CRITICAL - Fatal PE at up to 90 days from hospital discharge. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE (Dichotomous) CRITICAL - Clinically relevant non-major bleeding at up to 45 days from hospital discharge. Bleeding that does not meet the criteria for major bleed but requires

Review question	What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for acutely ill medical patients admitted to hospital?
	medical attention and/or a change in antithrombotic therapy (Dichotomous) IMPORTANT - Health-related quality of life (validated scores only) at up to 90 days from hospital discharge (Continuous) IMPORTANT - Heparin-induced thrombocytopenia at up to 90 days from hospital discharge (Dichotomous) IMPORTANT - Technical complications of mechanical interventions at up to 90 days from hospital discharge (Continuous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Other exclusions	People with suspected or confirmed venous thromboembolism Community settings and hospices, except when continuing prophylaxis that has been started in hospital Secondary prevention of VTE Early mobilisation and leg exercises People who are contraindicated for pharmacological and mechanical prophylaxis
Population stratification	People who are contraindicated for mechanical prophylaxis People who are contraindicated for pharmacological prophylaxis
Reasons for stratification	People who are contraindicated for pharmacological/mechanical prophylaxis are not able to undergo pharmacological/mechanical prophylaxis and so cannot be lumped together with people who are not contraindicated. People who are contraindicated for both pharmacological and mechanical prophylaxis are excluded from this review as a separate review will be conducted on this population.
Sensitivity/other analysis	Vitamin K Antagonists (warfarin, acenocoumarol and phenindione) will be combined for the analysis LMWH licensed in the UK (dalteparin, tinzaparin, enoxaparin) will be combined for the analysis LMWH not licensed in the UK (Bemiparin, Certoparin, Nadroparin, Parnaparin, Reviparin) will be combined for the analysis
Subgroup analyses if there is heterogeneity	- BMI (Mixed; Obese (BMI over 30 kg/m2); Severely obese (BMI over 35 kg/m2); Not obese (BMI under 30 kg/m2)); People who are obese (BMI over 30 kg/m2) and severely obese (BMI over 35 kg/m2) are at higher risk of VTE and major bleeding - Renal impairment (Renal impairment (eGFR less than 45 ml/min/1.73m2); No renal impairment (eGFR greater than 45 ml/min/1.73m2)); People with renal impairment (estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m2) are at higher risk of VTE and major bleeding - Mobility (Mobile; Totally immobile); People who are immobile are at higher risk of VTE
Search criteria	Databases: Medline, Embase, The Cochrane Library Date limits for search: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008 Language: Studies published in English language only

C.14 Cancer

Table 19: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with cancer having day procedures?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people being treated for cancer who are having day procedures?
Objectives	To find the most effective strategy for preventing VTE in people being treated for cancer who are having day procedures
Population	Adults and young people (16 years and older) with cancer who are having day procedures Active cancer defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma.
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)*

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people being treated for cancer who are having day procedures?
	Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 180 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-180 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7-180 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 180 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Studies where people received or were assumed to have received treatment for their conditions that is not used in current practice Community settings and hospices, except when continuing prophylaxis that has been started in hospital People with suspected or confirmed venous thromboembolism Secondary prevention of VTE

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people being treated for cancer who are having day procedures?
	Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: • LMWH • Vitamin K Antagonists Outcomes reported at different time points will be analysed together GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness.
Stratification	People who are contraindicated for pharmacological prophylaxis People who are contraindicated for mechanical prophylaxis
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Chemotherapy Tumour (solid; haematological)
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.15 Patients with central venous catheters

Table 20: Review protocol: What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for people with central venous catheters?

Review question	What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for people with central venous catheters?
Objectives	To find the most effective strategy for preventing VTE in people admitted to or discharged from hospital with central venous catheters
Population	Adults and young people (16 years and older) with central venous catheters who are: Admitted to hospital Discharged from hospital Outpatients
Interventions	Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*)

Review question	What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for people with central venous catheters?
	tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300 mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days after line removed) (NMA outcome) Deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days after line removed). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (up to 90 days after line removed). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days after line removed). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2 g/dL; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (up to 90 days after line removed). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes:

Review question	What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for people with central venous catheters?
	Clinically relevant non-major bleeding (up to 45 days after line removed): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days after line removed) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Community settings and hospices, except when continuing prophylaxis that has been started in hospital People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30 kg/m^2); obese (BMI over 30 kg/m^2); severely obese (BMI over 35 kg/m^2); Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness For major bleeding and clinically relevant non-major bleeding outcomes measured at 46 to 90 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.16 Palliative care

Table 21: Review protocol: People who are having palliative care

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are having palliative care?
Objectives	To find the most effective strategy for preventing VTE in people admitted to and discharged from hospital who are having palliative care
Population	Adults and young people (16 years and older) admitted to hospital and discharged from who are having palliative care. Definition from NHS the More Care, Less Pathway review: palliative care focuses on the relief of pain and other symptoms and problems experienced in serious illness. The goal of palliative care is to improve quality of life, by increasing comfort, promoting dignity and providing a support system to the person who is ill and those close to them.
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Vena caval filters Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)*

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are having palliative care?
	*off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH
Outcomes	Critical outcomes: Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Important outcomes: All-cause mortality (up to 90 days from hospital discharge) Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Community settings and hospices, except when continuing prophylaxis that has been started in hospital People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are having palliative care?
	Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated End of life care (last days of life 2-3 days; last year of life)
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.17 Critical care

Table 22: Review protocol: People admitted to intensive care units

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people admitted to intensive care units?
Objectives	To find the most effective strategy for preventing VTE in people admitted to intensive care units
Population	Adults and young people (16 years and older) admitted to intensive care units
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Vena caval filters Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people admitted to intensive care units?
	units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days after leaving ICU) Deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days after leaving ICU). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (up to 90 days after leaving ICU). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days after leaving ICU). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people admitted to intensive care units?
	need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (up to 90 days after leaving ICU). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days after leaving ICU): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 after leaving ICU) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study) Line associated thrombosis (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Intensive care units
Exclusions	Community settings and hospices, except when continuing prophylaxis that has been started in hospital People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer Surgical; medical; trauma
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people admitted to intensive care units?
	thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.18 Pregnant women and women up to 6 weeks postpartum

Table 23: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for pregnant women admitted to hospital (including up to 6 weeks after giving birth)?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for pregnant women admitted to hospital (including up to 6 weeks after giving birth)?
Objectives	To find the most effective strategy for preventing VTE in pregnant women admitted to hospital (including up to 6 weeks after giving birth)
Population	Pregnant women (including up to 6 weeks after giving birth) who are: • Admitted to hospital for 24 hours or more • Having day procedures including early pregnancy loss (miscarriage and termination)

Interventions	Mechanical:
	• Anti-embolism stockings (AES) (above or below knee)
	• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)
	• Foot pumps or foot impulse devices (FID)
	• Electrical stimulation (including Geko devices)
	• Continuous passive motion
	
	Pharmacological:
	• Unfractionated heparin (UFH) (low dose, administered subcutaneously)
	  ○ Low dose 5000 units three times a day, except in third trimester this may increase to 10,000 twice a day
	• Low molecular weight heparin (LMWH), licensed in UK:
	  ○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)
	  ○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum total daily dose 10000 *; obese patients – maximum 15000 units daily*)
	  ○ tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*)
	• LMWH, licensed in countries other than UK:
	  ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)
	  ○ Certoparin (3000 units daily)

	○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) ○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) ○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) • Fondaparinux (all doses) • Danaperoid (used in people with heparin allergy) • Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: • Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) • No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Short versus extended duration prophylaxis • Weight adjusted versus non-weight adjusted
Outcomes	Critical outcomes: • All-cause mortality (up to 90 days from hospital discharge) • Deep vein thrombosis (symptomatic and asymptomatic) (inpatient and up to 90 days from hospital discharge) . Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) • Pulmonary embolism (Inpatient and up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE • Major bleeding (inpatient and up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death (including foetal death); occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of red blood cells; leads to a drop in haemoglobin of ≥20g/l; a serious or life threatening clinical event (including having an adverse effect on the foetus). Includes unplanned visit to theatre for control of bleeding. • Fatal PE (inpatient and up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy (including the foetus). • Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	• Secondary care (including midwifery units) • Primary and community care when continuing prophylaxis after hospital

	discharge
Exclusions	• Initiation of prophylaxis in community settings and hospices • People with suspected or confirmed venous thromboembolism • Secondary prevention of arterial and venous thromboembolism • Early mobilisation and leg exercises • Non-English studies • Duration of follow-up <7 days; >150 days
Review strategy	• Outcomes reported at different time points will be analysed together • Doses of LMWH will be analysed together • GRADE assessments will be conducted • Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness
Stratification	• People who are contraindicated for pharmacological prophylaxis • People who are contraindicated for mechanical prophylaxis • Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage) • Pregnant or postpartum women not undergoing surgery
Subgroup analyses if there is heterogeneity	• BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) • Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) • Assisted conception (assisted vs non-assisted pregnancy) • LMWH doses (high, standard, low)
Search strategy	Databases: • Medline, Embase, The Cochrane Library Date limits: • Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). • Final search date for CG92: 10 December 2008

C.19 People with psychiatric illness

Table 24: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with psychiatric disorders?

Review question	**What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with psychiatric disorders?**
Guideline condition and its definition	VTE prophylaxis. Definition: Prevention of VTE in people admitted to and discharged from hospital, and people undergoing day procedures
Objectives	To find the most effective strategy for preventing VTE in people with psychiatric disorders
Review population	Adults and young people (16 years and older) with psychiatric disorders who are: • Admitted to hospital, psychiatric hospital or residential psychiatric unit • Having day procedures (for example electroconvulsive therapy) • Outpatients post-discharge

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with psychiatric disorders?
Pulmonary embolism	Adults Young people (aged 16 years or over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Anti-embolism stockings; Above knee Anti-embolism stockings; Below knee Anti-embolism stockings; Mixed above/below knee Intermittent pneumatic compression devices ; Full leg Intermittent pneumatic compression devices ; Below knee Intermittent pneumatic compression devices ; Mixed full leg/below knee Foot pumps or foot impulse devices ; Foot pumps Foot pumps or foot impulse devices ; Foot impulse Electrical stimulation Continuous passive motion Unfractionated heparin ; Unfractionated heparin (low dose, administered subcutaneously) Low molecular weight heparin (licensed in UK); Dalteparin (1,250 units once daily - 5,000 units twice daily) Low molecular weight heparin (licensed in UK); Tinzaparin (2,500 units once daily – 9,000 units once daily) Low molecular weight heparin (licensed in UK); Enoxaparin (20mg once daily – 60mg twice daily) Vitamin K antagonists ; Warfarin (all doses) Vitamin K antagonists ; Acenocoumarol (all doses) Vitamin K antagonists ; Phenindione (all doses) Fondaparinux; Fondaparinux (all doses) Apixaban; Apixaban (all doses) Dabigatran; Dabigatran (all doses) Rivaroxaban; Rivaroxaban (all doses) Aspirin; Aspirin (up to 300mg) No treatment; Usual care No treatment; Placebo Low molecular weight heparin (not licensed in UK); Bemiparin (2500 units once daily - 3500 units once daily) Low molecular weight heparin (not licensed in UK); Certoparin (3000 units once daily) Low molecular weight heparin (not licensed in UK); Nadroparin (2850 units once daily - up to 57 units/kg once daily) Low molecular weight heparin (not licensed in UK); Parnaparin (3200 units once daily - 4250 units once daily) Low molecular weight heparin (not licensed in UK); Reviparin (1750 units once daily - 4200 units once daily)
Outcomes	- All-cause mortality at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular,

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with psychiatric disorders?
	retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge (Dichotomous) CRITICAL - Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge (Dichotomous) IMPORTANT - Health-related quality of life (validated scores only) at up to 90 days from hospital discharge (Continuous) IMPORTANT - Heparin-induced thrombocytopenia at duration of study (Dichotomous) IMPORTANT - Technical complications of mechanical interventions at duration of study (Continuous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Other exclusions	People with suspected or confirmed venous thromboembolism Community settings and hospices, except when continuing prophylaxis that has been started in hospital Secondary prevention of VTE Early mobilisation and leg exercises People who are contraindicated for pharmacological and mechanical prophylaxis
Population stratification	People who are contraindicated for mechanical prophylaxis People who are contraindicated for pharmacological prophylaxis
Reasons for stratification	People who are contraindicated for pharmacological/mechanical prophylaxis are not able to undergo pharmacological/mechanical prophylaxis and so cannot be lumped together with people who are not contraindicated. People who are contraindicated for both pharmacological and mechanical prophylaxis are excluded from this review as a separate review will be conducted on this population.
Other stratifications	None
Sensitivity/other analysis	Vitamin K Antagonists (warfarin, acenocoumarol and phenindione) will be combined for the analysis LMWH licensed in the UK (dalteparin, tinzaparin, enoxaparin) will be combined for the analysis LMWH not licensed in the UK (Bemiparin, Certoparin, Nadroparin, Parnaparin, Reviparin) will be combined for the analysis
Subgroup analyses if there is heterogeneity	- BMI (Mixed; Obese (BMI over 30 kg/m2); Severely obese (BMI over 35 kg/m2); Not obese (BMI under 30 kg/m2)); People who are obese (BMI over 30 kg/m2) and severely obese (BMI over 35 kg/m2) are at higher risk of VTE and major bleeding - Renal impairment (Renal impairment (eGFR less than 30 ml/min/1.73m2); No renal impairment (eGFR greater than 30ml/min/1.73m2)); People with renal

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with psychiatric disorders?
	impairment (estimated glomerular filtration rate (eGFR) of less than 30ml/min/1.73m2) are at higher risk of VTE and major bleeding -Antipsychotic use (Antipsychotic use; no antipsychotic use) -Mobility (Catatonic/immobile; mobile)
Search criteria	Databases: Medline, Embase, The Cochrane Library Date limits for search: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008 Language: Studies published in English language only

C.20 Anaesthesia

None

C.21 Lower limb immobilisation

Table 25: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people with lower limb immobilisation?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people with lower limb immobilisation?
Objectives	To find the most effective strategy for preventing VTE in people with lower limb immobilisation
Population	Adults and young people (16 years and older) with lower limb immobilisation who are: Admitted to hospital Having day procedures Outpatients post-discharge Immobilisation is defined as any clinical decision taken to manage the affected limb in such a way as to prevent normal weight bearing status and/or use of that limb.
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*)

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people with lower limb immobilisation?
	LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum (according to the preference of the hosunits once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge. Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes:

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people with lower limb immobilisation?
	Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study) Unplanned return to theatre (up to 45 days from hospital discharge)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Studies where people received or were assumed to have received treatment for their conditions that is not used in current practice Community settings and hospices, except when continuing prophylaxis that has been started in hospital People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness. For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness Network-meta analysis will be conducted for the outcomes specified above where possible.
Stratification	People who are contraindicated for pharmacological prophylaxis People who are contraindicated for mechanical prophylaxis
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2); obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer Weight bearing; non-weight bearing
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.22 Fragility fractures of the pelvis, hip and proximal femur

Table 26: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with fragility fractures of the pelvis, hip or proximal femur?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with fragility fractures of the pelvis, hip or proximal femur?
Guideline condition and its definition	VTE prophylaxis. Definition: Prevention of VTE in people admitted to and discharged from hospital, and people undergoing day procedures
Objectives	To find the most effective strategy for preventing VTE in people with fragility fractures of the pelvis, hip or proximal femur
Review population	Adults and young people (16 years and older) with fragility fractures of the pelvis, hip or proximal femur
	Adults Young people (aged 16 years or over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Anti-embolism stockings; Above knee Anti-embolism stockings; Below knee Anti-embolism stockings; Mixed above/below knee Intermittent pneumatic compression devices ; Full leg Intermittent pneumatic compression devices ; Below knee Intermittent pneumatic compression devices ; Mixed full leg/below knee Foot pumps or foot impulse devices ; Foot pumps Foot pumps or foot impulse devices ; Foot impulse Electrical stimulation Continuous passive motion Vena cava filters Unfractionated heparin ; Unfractionated heparin (low dose, administered subcutaneously) Low molecular weight heparin (licensed in UK); Dalteparin (1,250 units once daily - 5,000 units twice daily) Low molecular weight heparin (licensed in UK); Tinzaparin (2,500 units once daily – 9,000 units once daily) Low molecular weight heparin (licensed in UK); Enoxaparin (20mg once daily – 60mg twice daily) Vitamin K antagonists ; Warfarin (all doses) Vitamin K antagonists ; Acenocoumarol (all doses) Vitamin K antagonists ; Phenindione (all doses) Fondaparinux; Fondaparinux (all doses) Apixaban; Apixaban (all doses) Dabigatran; Dabigatran (all doses) Rivaroxaban; Rivaroxaban (all doses) Aspirin; Aspirin (up to 300mg) No treatment; Usual care No treatment; Placebo Low molecular weight heparin (not licensed in UK); Bemiparin (2500 units once daily - 3500 units once daily) Low molecular weight heparin (not licensed in UK); Certoparin (3000 units once daily) Low molecular weight heparin (not licensed in UK); Nadroparin (2850 units once daily - up to 57 units/kg once daily)

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with fragility fractures of the pelvis, hip or proximal femur?
	Low molecular weight heparin (not licensed in UK); Parnaparin (3200 units once daily - 4250 units once daily) Low molecular weight heparin (not licensed in UK); Reviparin (1750 units once daily - 4200 units once daily)
Outcomes	- All-cause mortality at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge (Dichotomous) CRITICAL - Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge (Dichotomous) IMPORTANT - Health-related quality of life (validated scores only) at up to 90 days from hospital discharge (Continuous) IMPORTANT - Heparin-induced thrombocytopenia at duration of study (Dichotomous) IMPORTANT - Technical complications of mechanical interventions at duration of study (Continuous) IMPORTANT - Infection at duration of study (Dichotomous) IMPORTANT - VTE at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - DVT (symptomatic) at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - DVT (distal) at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - DVT (proximal) at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - Fatal bleeding at 45 days from hospital discharge (Dichotomous) ADDITIONAL - Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge (Dichotomous) ADDITIONAL
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Follow-up <7 days
Other exclusions	People with suspected or confirmed venous thromboembolism Community settings and hospices, except when continuing prophylaxis that has been started in hospital Secondary prevention of VTE

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with fragility fractures of the pelvis, hip or proximal femur?
	Early mobilisation and leg exercises People who are contraindicated for pharmacological and mechanical prophylaxis Non-English studies Duration of follow-up <7 days or >150 days
Population stratification	People who are contraindicated for mechanical prophylaxis People who are contraindicated for pharmacological prophylaxis
Reasons for stratification	People who are contraindicated for pharmacological/mechanical prophylaxis are not able to undergo pharmacological/mechanical prophylaxis and so cannot be lumped together with people who are not contraindicated. People who are contraindicated for both pharmacological and mechanical prophylaxis are excluded from this review as a separate review will be conducted on this population.
Other stratifications	People who are contraindicated
Sensitivity/other analysis	Vitamin K Antagonists (warfarin, acenocoumarol and phenindione) will be combined for the analysis LMWH licensed in the UK (dalteparin, tinzaparin, enoxaparin) will be combined for the analysis LMWH not licensed in the UK (Bemiparin, Certoparin, Nadroparin, Parnaparin, Reviparin) will be combined for the analysis
Subgroup analyses if there is heterogeneity	- BMI (Mixed; Obese (BMI over 30 kg/m2); Severely obese (BMI over 35 kg/m2); Not obese (BMI under 30 kg/m2)); People who are obese (BMI over 30 kg/m2) and severely obese (BMI over 35 kg/m2) are at higher risk of VTE and major bleeding - Renal impairment (Renal impairment (eGFR less than 30 ml/min/1.73m2); No renal impairment (eGFR greater than 30ml/min/1.73m2)); People with renal impairment (estimated glomerular filtration rate (eGFR) of less than 30ml/min/1.73m2) are at higher risk of VTE and major bleeding - Cancer status (Not applicable; Not stated / Unclear; Active cancer (defines as receiving active anti-mitotic treatment, or was diagnosed in the last 6 months, or recurrent or metastatic, or where tumour is inoperable. Excludes squamous skin cancer and basel cell carcinoma); No active cancer); People with active cancer are at higher risk of VTE - Immobilisation (Internal fixation/immobilisaton; No fixation/immobilisation); People with fixation/immobilisation are at higher risk of VTE due to reduced mobility
Search criteria	Databases: Medline, Embase, The Cochrane Library Date limits for search: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008 Language: Studies published in English language only

C.23 Elective hip replacement

Table 27: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective hip replacement?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective hip replacement?
Guideline condition and its definition	VTE prophylaxis. Definition: Prevention of VTE in people admitted to and discharged from hospital, and people undergoing day procedures
Objectives	To find the most effective strategy for preventing VTE in people undergoing elective hip replacement
Review population	Adults and young people (16 years and older) undergoing elective hip replacement admitted to and discharged from hospital
	Adults Young people (aged 16 years or over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Anti-embolism stockings; Above knee Anti-embolism stockings; Below knee Anti-embolism stockings; Mixed above/below knee Intermittent pneumatic compression devices ; Full leg Intermittent pneumatic compression devices ; Below knee Intermittent pneumatic compression devices ; Mixed full leg/below knee Foot pumps or foot impulse devices ; Foot pumps Foot pumps or foot impulse devices ; Foot impulse Electrical stimulation Continuous passive motion Unfractionated heparin ; Unfractionated heparin (low dose, administered subcutaneously) Low molecular weight heparin (licensed in UK); Dalteparin (1,250 units once daily - 5,000 units twice daily) Low molecular weight heparin (licensed in UK); Tinzaparin (2,500 units once daily – 9,000 units once daily) Low molecular weight heparin (licensed in UK); Enoxaparin (20mg once daily – 60mg twice daily) Vitamin K antagonists ; Warfarin (all doses) Vitamin K antagonists ; Acenocoumarol (all doses) Vitamin K antagonists ; Phenindione (all doses) Fondaparinux; Fondaparinux (all doses) Apixaban; Apixaban (all doses) Dabigatran; Dabigatran (all doses) Rivaroxaban; Rivaroxaban (all doses) Aspirin; Aspirin (up to 300mg) No treatment; Usual care No treatment; Placebo Low molecular weight heparin (not licensed in UK); Bemiparin (2500 units once daily - 3500 units once daily) Low molecular weight heparin (not licensed in UK); Certoparin (3000 units once daily) Low molecular weight heparin (not licensed in UK); Nadroparin (2850 units once daily - up to 57 units/kg once daily) Low molecular weight heparin (not licensed in UK); Parnaparin (3200 units once daily - 4250 units once daily) Low molecular weight heparin (not licensed in UK); Reviparin (1750 units once daily - 4200 units once daily)

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective hip replacement?
Outcomes	- All-cause mortality at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge (Dichotomous) CRITICAL - Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge (Dichotomous) IMPORTANT - Surgical site haematoma at up to 45 days from hospital discharge (Dichotomous) CRITICAL - Health-related quality of life (validated scores only) at up to 90 days from hospital discharge (Continuous) IMPORTANT - Heparin-induced thrombocytopenia at duration of study (Dichotomous) IMPORTANT - Technical complications of mechanical interventions at duration of study (Continuous) IMPORTANT - Infection at duration of study (Dichotomous) IMPORTANT - VTE at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - DVT (symptomatic) at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - DVT (distal) at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - DVT (proximal) at 7-90 days from hospital discharge ADDITIONAL - Fatal bleeding at 45 days from hospital discharge (Dichotomous) ADDITIONAL - Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge (Dichotomous) ADDITIONAL
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Other exclusions	People with suspected or confirmed venous thromboembolism Community settings and hospices, except when continuing prophylaxis that has been started in hospital Secondary prevention of VTE Early mobilisation and leg exercises People who are contraindicated for pharmacological and mechanical prophylaxis

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective hip replacement?
Population stratification	People who are contraindicated for mechanical prophylaxis People who are contraindicated for pharmacological prophylaxis
Reasons for stratification	People who are contraindicated for pharmacological/mechanical prophylaxis are not able to undergo pharmacological/mechanical prophylaxis and so cannot be lumped together with people who are not contraindicated. People who are contraindicated for both pharmacological and mechanical prophylaxis are excluded from this review as a separate review will be conducted on this population.
Other stratifications	People who are contraindicated
Sensitivity/other analysis	Vitamin K Antagonists (warfarin, acenocoumarol and phenindione) will be combined for the analysis LMWH licensed in the UK (dalteparin, tinzaparin, enoxaparin) will be combined for the analysis LMWH not licensed in the UK (Bemiparin, Certoparin, Nadroparin, Parnaparin, Reviparin) will be combined for the analysis
Subgroup analyses if there is heterogeneity	- BMI (Mixed; Obese (BMI over 30 kg/m2); Severely obese (BMI over 35 kg/m2); Not obese (BMI under 30 kg/m2)); People who are obese (BMI over 30 kg/m2) and severely obese (BMI over 35 kg/m2) are at higher risk of VTE and major bleeding - Renal impairment (Renal impairment (eGFR less than 30 ml/min/1.73m2); No renal impairment (eGFR greater than 30ml/min/1.73m2)); People with renal impairment (estimated glomerular filtration rate (eGFR) of less than 30ml/min/1.73m2) are at higher risk of VTE and major bleeding
Search criteria	Databases: Medline, Embase, The Cochrane Library Date limits for search: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008 Language: Studies published in English language only

C.24 Elective knee replacement

Table 28: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective knee replacement?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective knee replacement?
Guideline condition and its definition	VTE prophylaxis. Definition: Prevention of VTE in people admitted to and discharged from hospital, and people undergoing day procedures
Objectives	To find the most effective strategy for preventing VTE in people undergoing elective knee replacement
Review population	Adults and young people (16 years and older) undergoing elective knee replacement admitted to and discharged from hospital
	Adults Young people (aged 16 years or over)

	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Anti-embolism stockings; Above knee Anti-embolism stockings; Below knee Anti-embolism stockings; Mixed above/below knee Intermittent pneumatic compression devices ; Full leg Intermittent pneumatic compression devices ; Below knee Intermittent pneumatic compression devices ; Mixed full leg/below knee Foot pumps or foot impulse devices ; Foot pumps Foot pumps or foot impulse devices ; Foot impulse Electrical stimulation Continuous passive motion Vena cava filters Unfractionated heparin ; Unfractionated heparin (low dose, administered subcutaneously) Low molecular weight heparin (licensed in UK); Dalteparin (1,250 units once daily - 5,000 units twice daily) Low molecular weight heparin (licensed in UK); Tinzaparin (2,500 units once daily – 9,000 units once daily) Low molecular weight heparin (licensed in UK); Enoxaparin (20mg once daily – 60mg twice daily) Vitamin K antagonists ; Warfarin (all doses) Vitamin K antagonists ; Acenocoumarol (all doses) Vitamin K antagonists ; Phenindione (all doses) Fondaparinux; Fondaparinux (all doses) Apixaban; Apixaban (all doses) Dabigatran; Dabigatran (all doses) Rivaroxaban; Rivaroxaban (all doses) Aspirin; Aspirin (up to 300mg) No treatment; Usual care No treatment; Placebo Low molecular weight heparin (not licensed in UK); Bemiparin (2500 units once daily - 3500 units once daily) Low molecular weight heparin (not licensed in UK); Certoparin (3000 units once daily) Low molecular weight heparin (not licensed in UK); Nadroparin (2850 units once daily - up to 57 units/kg once daily) Low molecular weight heparin (not licensed in UK); Parnaparin (3200 units once daily - 4250 units once daily) Low molecular weight heparin (not licensed in UK); Reviparin (1750 units once daily - 4200 units once daily)
Outcomes	- All-cause mortality at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge (Dichotomous) CRITICAL - Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography;

	clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge (Dichotomous) IMPORTANT - Surgical site haematoma at up to 45 days from hospital discharge (Dichotomous) CRITICAL - Health-related quality of life (validated scores only) at up to 90 days from hospital discharge (Continuous) IMPORTANT - Heparin-induced thrombocytopenia at duration of study (Dichotomous) IMPORTANT - Technical complications of mechanical interventions at duration of study (Continuous) IMPORTANT - Infection at duration of study (Dichotomous) IMPORTANT - VTE at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - DVT (symptomatic) at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - DVT (distal) at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - DVT (proximal) at 7-90 days from hospital discharge (Dichotomous) ADDITIONAL - Fatal bleeding at 45 days from hospital discharge (Dichotomous) ADDITIONAL - Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge (Dichotomous) ADDITIONAL
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Other exclusions	People with suspected or confirmed venous thromboembolism Community settings and hospices, except when continuing prophylaxis that has been started in hospital Secondary prevention of VTE Early mobilisation and leg exercises People who are contraindicated for both pharmacological and mechanical prophylaxis
Population stratification	People who are contraindicated for mechanical prophylaxis People who are contraindicated for pharmacological prophylaxis
Reasons for stratification	People who are contraindicated for pharmacological/mechanical prophylaxis are not able to undergo pharmacological/mechanical prophylaxis and so cannot be lumped together with people who are not contraindicated. People who are contraindicated for both pharmacological and mechanical prophylaxis are excluded from this review as a separate review will be conducted on this population.
Other stratifications	People who are contraindicated
Sensitivity/other analysis	Vitamin K Antagonists (warfarin, acenocoumarol and phenindione) will be combined for the analysis LMWH licensed in the UK (dalteparin, tinzaparin, enoxaparin) will be combined for the analysis LMWH not licensed in the UK (Bemiparin, Certoparin, Nadroparin, Parnaparin, Reviparin) will be combined for the analysis
Subgroup analyses if there is heterogeneity	- BMI (Mixed; Obese (BMI over 30 kg/m2); Severely obese (BMI over 35 kg/m2); Not obese (BMI under 30 kg/m2)); People who are obese (BMI over 30 kg/m2)

	and severely obese (BMI over 35 kg/m2) are at higher risk of VTE and major bleeding - Renal impairment (Renal impairment (eGFR less than 30 ml/min/1.73m2); No renal impairment (eGFR greater than 30ml/min/1.73m2)); People with renal impairment (estimated glomerular filtration rate (eGFR) of less than 30ml/min/1.73m2) are at higher risk of VTE and major bleeding
Search criteria	Databases: Medline, Embase, The Cochrane Library Date limits for search: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008 Language: Studies published in English language only

C.25 Non-arthroplasty orthopaedic knee surgery

Table 29: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having non-arthroplasty knee surgery?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having non-arthroplasty knee surgery?
Objectives	To find the most effective strategy for preventing VTE in people having non-arthroplasty knee surgery (including knee arthroscopy , osteotomy and peri-articular trauma)
Population	Adults and young people (16 years and older) having non-arthroplasty knee surgery who are: • Admitted to hospital • Having day procedures • Outpatients post-discharge

Interventions	Mechanical:
	• Anti-embolism stockings (AES) (above or below knee)
	• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)
	• Foot pumps or foot impulse devices (FID)
	• Electrical stimulation (including Geko devices)
	• Continuous passive motion
	
	Pharmacological:
	• Unfractionated heparin (UFH) (low dose, administered subcutaneously)
	• Low molecular weight heparin (LMWH), licensed in UK:
	  ○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)
	  ○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*)
	  ○ tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*)
	• LMWH, licensed in countries other than UK:
	  ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having non-arthroplasty knee surgery?
	to maximum 3500 units daily) ○ Certoparin (3000 units daily) ○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) ○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) ○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) • Vitamin K Antagonists: ○ warfarin (variable dose only) ○ acenocoumarol (all doses) ○ phenindione (all doses) • Fondaparinux (all doses)* • Apixaban (all doses)* • Dabigatran (all doses)* • Rivaroxaban (all doses)* • Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: • Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) • No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Standard versus extended duration prophylaxis • Low versus high dose for LMWH • Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: • All-cause mortality (up to 90 days from hospital discharge) • Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge. Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) • Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE • Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding • Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having non-arthroplasty knee surgery?
	including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. • Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study) • Unplanned return to theatre (up to 45 days from hospital discharge)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs
Settings	• Primary and community care when continuing prophylaxis after hospital discharge • Secondary care
Exclusions	• Studies where people received or were assumed to have received treatment for their conditions that is not used in current practice • People with knee arthroplasty • Community settings and hospices, except when continuing prophylaxis that has been started in hospital • People with suspected or confirmed venous thromboembolism • Secondary prevention of VTE • Early mobilisation and leg exercises • Non-English studies • Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: • LMWH • Vitamin K Antagonists Outcomes reported at different time points will be analysed together GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness. For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Stratification	• People who are contraindicated for pharmacological prophylaxis • People who are contraindicated for mechanical prophylaxis • Major arthroscopic surgery (combined anaesthetic and surgery longer than 1 hour) • Minor arthroscopic surgery (combined anaesthetic and surgery less than 1 hour) • Osteotomy • Peri-articular trauma
Subgroup analyses if there is	• BMI: not obese (BMI under 30kg/m2); obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2)

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having non-arthroplasty knee surgery?
heterogeneity	• Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) • Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer
Search strategy	Databases: • Medline, Embase, The Cochrane Library Date limits: • Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). • Final search date for CG92: 10 December 2008

C.26 Foot and ankle orthopaedic surgery

Table 30: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having foot and ankle surgery?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having foot and ankle surgery?
Objectives	To find the most effective strategy for preventing VTE in people having foot and ankle surgery
Population	Adults and young people (16 years and older) having foot and ankle surgery who are: Admitted to hospital Having day procedures Outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily)

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having foot and ankle surgery?
	Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge. Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study)

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having foot and ankle surgery?
	Technical complications of mechanical interventions (duration of study) Unplanned return to theatre (up to 45 days from hospital discharge)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Studies where people received or were assumed to have received treatment for their conditions that is not used in current practice Community settings and hospices, except when continuing prophylaxis that has been started in hospital People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness. For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Stratification	People who are contraindicated for pharmacological prophylaxis People who are contraindicated for mechanical prophylaxis
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2); obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer Achilles tendon (elective and injury)
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.27 Upper limb orthopaedic surgery

Table 31: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having upper limb surgery?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having upper limb surgery?
Objectives	To find the most effective strategy for preventing VTE in people having upper limb surgery
Population	Adults and young people (16 years and older) having upper limb surgery who are: Admitted to hospital Having day procedures Outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having upper limb surgery?
	(between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge. Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study) Unplanned return to theatre (up to 45 days from hospital discharge) Upper limb DVT (7-90 days from hospital discharge. Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Studies where people received or were assumed to have received treatment for their conditions that is not used in current practice Community settings and hospices, except when continuing prophylaxis that has been started in hospital People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having upper limb surgery?
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness. For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Stratification	People who are contraindicated for pharmacological prophylaxis People who are contraindicated for mechanical prophylaxis Major (anaesthetic and surgery longer than 90 minutes) Minor (anaesthetic and surgery less than 90 minutes)
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2); obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.28 Spinal surgery

Table 32: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing spinal surgery?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing spinal surgery?
Guideline condition and its definition	VTE prophylaxis. Definition: Prevention of VTE in people admitted to and discharged from hospital, and people undergoing day procedures
Objectives	To find the most effective strategy for preventing VTE in people undergoing spinal surgery
Review population	Adults and young people (16 years and older) undergoing spinal surgery who are admitted to hospital, having day procedures, and outpatients post-discharge
	Adults Young people (aged 16 years or over)
	Line of therapy not an inclusion criterion

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing spinal surgery?
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Anti-embolism stockings; Above knee Anti-embolism stockings; Below knee Anti-embolism stockings; Mixed above/below knee Intermittent pneumatic compression devices ; Full leg Intermittent pneumatic compression devices ; Below knee Intermittent pneumatic compression devices ; Mixed full leg/below knee Foot pumps or foot impulse devices ; Foot pumps Foot pumps or foot impulse devices ; Foot impulse Electrical stimulation Continuous passive motion Unfractionated heparin ; Unfractionated heparin (low dose, administered subcutaneously) Low molecular weight heparin (licensed in UK); Dalteparin (1,250 units once daily - 5,000 units twice daily) Low molecular weight heparin (licensed in UK); Tinzaparin (2,500 units once daily – 9,000 units once daily) Low molecular weight heparin (licensed in UK); Enoxaparin (20mg once daily – 60mg twice daily) Vitamin K antagonists ; Warfarin (variable dose) Vitamin K antagonists ; Acenocoumarol (all doses) Vitamin K antagonists ; Phenindione (all doses) Fondaparinux; Fondaparinux (all doses) Apixaban; Apixaban (all doses) Dabigatran; Dabigatran (all doses) Rivaroxaban; Rivaroxaban (all doses) Aspirin; Aspirin (up to 300mg) No treatment; Usual care No treatment; Placebo Low molecular weight heparin (not licensed in UK); Bemiparin (2500 units once daily - 3500 units once daily) Low molecular weight heparin (not licensed in UK); Certoparin (3000 units once daily) Low molecular weight heparin (not licensed in UK); Nadroparin (2850 units once daily - up to 57 units/kg once daily) Low molecular weight heparin (not licensed in UK); Parnaparin (3200 units once daily - 4250 units once daily) Low molecular weight heparin (not licensed in UK); Reviparin (1750 units once daily - 4200 units once daily)
Outcomes	- All-cause mortality at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge (Dichotomous) CRITICAL - Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge (Dichotomous) CRITICAL - Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram;

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing spinal surgery?
	ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge (Dichotomous) CRITICAL - Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge (Dichotomous) IMPORTANT - Health-related quality of life (validated scores only) at up to 90 days from hospital discharge (Continuous) IMPORTANT - Heparin-induced thrombocytopenia at duration of study (Dichotomous) IMPORTANT - Technical complications of mechanical interventions at duration of study (Continuous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	7 days
Other exclusions	People with suspected or confirmed venous thromboembolism Community settings and hospices, except when continuing prophylaxis that has been started in hospital Secondary prevention of VTE Early mobilisation and leg exercises Study not published in English Duration of follow up >150 days Studies where people received or were assumed to have received treatment for their conditions that is not used in current practice
Population stratification	People who are contraindicated for mechanical prophylaxis People who are contraindicated for pharmacological prophylaxis Spinal injections Vertebroplasty and kyphoplasty
Reasons for stratification	People who are contraindicated for pharmacological/mechanical prophylaxis are not able to undergo pharmacological/mechanical prophylaxis and so cannot be lumped together with people who are not contraindicated. People who are contraindicated for both pharmacological and mechanical prophylaxis are excluded from this review as a separate review will be conducted on this population.
Sensitivity/other analysis	Vitamin K Antagonists will be combined for the analysis LMWH will be combined for the analysis
Subgroup analyses if there is heterogeneity	- BMI (Mixed; Obese (BMI over 30 kg/m2); Severely obese (BMI over 35 kg/m2); Not obese (BMI under 30 kg/m2)); People who are obese (BMI over 30 kg/m2) and severely obese (BMI over 35 kg/m2) are at higher risk of VTE and major bleeding - Renal impairment (Renal impairment (eGFR less than 30 ml/min/1.73m2); No renal impairment (eGFR greater than 30ml/min/1.73m2)); People with renal impairment (estimated glomerular filtration rate (eGFR) of less than 30ml/min/1.73m2) are at higher risk of VTE and major bleeding - Active cancer (Not applicable; Not stated / Unclear; Active cancer; No active cancer); to be added

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing spinal surgery?
	- Weight bearing (Weight bearing; Non-weight bearing); to be added
Search criteria	Databases: Medline, Embase, The Cochrane Library Date limits for search: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008 Language: Studies published in English language only

C.29 Cranial surgery

Table 33: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing intracranial surgery?

Review protocol	
Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing intracranial surgery?
Objectives	To find the most effective strategy for preventing VTE in people undergoing intra-cranial surgery
Population	Adults and young people (16 years and older) who are having intracranial surgery who are admitted to hospital, having day procedures or outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Pharmacological (no minimum duration): Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)

Review protocol	
	Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose), acenocoumarol (all doses), phenindione (all doses) Fondaparinux (all doses) Apixaban (all doses) Dabigatran (all doses) Rivaroxaban (all doses) Aspirin (up to 300 mg)
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge Low versus high dose for LMWH only Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7–90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7–90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2 g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7–90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care

Review protocol	
Exclusions	People with stroke (sub arachnoid haemorrhage that results in neurological impairment) Community settings and hospices, except when continuing prophylaxis that has been started in hospital People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness. For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Stratification	People who are contraindicated for pharmacological prophylaxis People who are contraindicated for mechanical prophylaxis People with intracranial tumour having neurosurgery [population must be >80% tumour]
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30 kg/m^2); obese (BMI over 30 kg/m^2); severely obese (BMI over 35 kg/m^2); Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer Immobility; mobile
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.30 Spinal injury

Table 34: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with spinal injury?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with spinal injury?
Objectives	To find the most effective strategy for preventing VTE in people with spinal cord or spinal

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with spinal injury?
	column injury
Population	Adults and young people (16 years and older) with cord or spinal column injury who are: Admitted to hospital Outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500-4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with spinal injury?
	Full leg versus below knee IPC devices Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2 g/dl; a serious or life threatening clinical event. Includes returning to theatre for surgery for control of bleeding and epidural bleeding Fatal PE (7–90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care Specialist rehab hospitals
Exclusions	Community settings and hospices, except when continuing prophylaxis that has been started in hospital People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together GRADE assessments will be conducted Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with spinal injury?
	For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Stratification	People who are contraindicated
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30 kg/m^2) obese (obesity I and II, 30–34.9 kg/m^2); severely obese (obesity III, ≥40 kg/m^2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer Isolated spinal injury; multiple injury
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.31 Major trauma

Table 35: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with major trauma?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with major trauma?
Objectives	To find the most effective strategy for preventing VTE in people with major trauma
Population	Adults and young people (16 years and older) who are attending hospital with major trauma (major trauma defined as Injury Severity Score ≥16) and outpatients post-discharge
Interventions	Mechanical: • Anti-embolism stockings (above or below knee) • Intermittent pneumatic compression (IPCD) devices (full leg or below knee) • Foot pumps or foot impulse devices (FID) • Electrical stimulation (including Geko devices) • Continuous passive motion • Vena caval filters Pharmacological: • Unfractionated heparin (UFH) (low dose, administered subcutaneously) • Low molecular weight heparin (LMWH), licensed in UK: ○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*) ○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) ○ tinzaparin (standard prophylactic dose 3500-4500 units once daily; minimum 2500

	units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) • LMWH, licensed in countries other than UK: ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) ○ Certoparin (3000 units daily) ○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) ○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) ○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) • Vitamin K Antagonists: ○ warfarin (variable dose only) ○ acenocoumarol (all doses) ○ phenindione (all doses) • Fondaparinux (all doses)* • Apixaban (all doses)* • Dabigatran (all doses)* • Rivaroxaban (all doses)* • Aspirin (up to 300 mg)* *off-label
Comparisons	Compared to: • Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) • No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge • Low versus high dose for LMWH • Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: • All-cause mortality (up to 90 days from hospital discharge) • Deep vein thrombosis (symptomatic and asymptomatic) (7–90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) • Pulmonary embolism (7–90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE • Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2 g/dl; a serious or life threatening clinical event. Includes returning to theatre for surgery for control of bleeding. • Fatal PE (7–90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE

	Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. • Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	• Primary and community care when continuing prophylaxis after hospital discharge • Secondary care • Specialist rehab hospitals
Exclusions	• Community settings and hospices, except when continuing prophylaxis that has been started in hospital • People with suspected or confirmed venous thromboembolism • Secondary prevention of VTE • Early mobilisation and leg exercises • Non-English studies • Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: • LMWH • Vitamin K Antagonists Outcomes reported at different time points will be analysed together GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness. For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Stratification	• People who are contraindicated for pharmacological prophylaxis • People who are contraindicated for mechanical prophylaxis
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30 kg/m^2) obese (obesity I and II, 30–34.9 kg/m^2); severely obese (obesity III, ≥40 kg/m^2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.32 Abdominal surgery (excluding bariatric surgery)

Table 36: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing abdominal surgery (gastrointestinal, gynaecological, urological)?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing abdominal surgery (gastrointestinal, gynaecological, urological)?
Objectives	To find the most effective strategy for preventing VTE in people undergoing abdominal surgery who are admitted to and discharged from hospital
Population	Adults and young people (16 years and older) undergoing abdominal surgery (including gynaecology) who are admitted to hospital, and outpatients post-discharge

Interventions	Mechanical:
	• Anti-embolism stockings (AES) (above or below knee)
	• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)
	• Foot pumps or foot impulse devices (FID)
	• Electrical stimulation (including Geko devices)
	• Continuous passive motion
	
	Pharmacological (no minimum duration):
	• Unfractionated heparin (UFH) (low dose, administered subcutaneously)
	• Low molecular weight heparin (LMWH), licensed in UK:
	• Low molecular weight heparin (LMWH), licensed in UK:
	  ○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)
	  ○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*)
	  ○ tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*)
	• LMWH, licensed in countries other than UK:
	  ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)
	  ○ Certoparin (3000 units daily)
	  ○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)
	  ○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)
	  ○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)
	• Vitamin K Antagonists: warfarin (variable dose), acenocoumarol (all doses), phenindione (all doses)
	• Fondaparinux (all doses)
	• Apixaban (all doses)
	• Dabigatran (all doses)
	• Rivaroxaban (all doses)
	• Aspirin (up to 300mg)*
	
	*off-licence

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing abdominal surgery (gastrointestinal, gynaecological, urological)?
Comparisons	Compared to: • Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) • No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge • Low versus high dose for LMWH
Outcomes	Critical outcomes: • All-cause mortality (up to 90 days from hospital discharge) (NMA outcome) • Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) (NMA outcome) • Pulmonary embolism (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE (NMA outcome) • Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (NMA outcome) • Fatal PE (up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy • Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Studies where people received or were assumed to have received treatment for their conditions that is not used in current practice Thoracic surgery Bariatric surgery

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing abdominal surgery (gastrointestinal, gynaecological, urological)?
	People with suspected or confirmed venous thromboembolism Community settings and hospices, except when continuing prophylaxis that has been started in hospital Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of study <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together Outcomes reported pre- and post-operative discharge will be analysed together GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness. For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness Network-meta analysis will be conducted for the outcomes specified above where possible.
Stratification	People who are contraindicated for pharmacological prophylaxis People who are contraindicated for mechanical prophylaxis
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer Acute; elective Laparoscopic surgery; open surgery
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.33 Bariatric surgery

Table 37: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing bariatric surgery?

Review protocol	
Objectives	To find the most effective strategy for preventing VTE in people undergoing bariatric surgery who are admitted to and discharged from hospital
Population	Adults and young people (16 years and older) undergoing bariatric surgery who are admitted to hospital, and outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Pharmacological (no minimum duration): Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose), acenocoumarol (all doses), phenindione (all doses) Fondaparinux (all doses) Apixaban (all doses) Dabigatran (all doses) Rivaroxaban (all doses) Aspirin (up to 300mg)
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings

Review protocol	
	Full leg versus below knee IPC devices Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge Low versus high dose for LMWH licensed in UK only Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) (NMA outcome) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool). Pulmonary embolism (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event Fatal PE (up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Studies where people received or were assumed to have received treatment for their conditions that is not used in current practice People with suspected or confirmed venous thromboembolism Community settings and hospices, except when continuing prophylaxis that has been started in hospital Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together Outcomes reported pre- and post-operative discharge will be analysed together

Review protocol	
	GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness. For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness.
Stratification	People who are contraindicated for pharmacological prophylaxis People who are contraindicated for mechanical prophylaxis
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.34 Cardiac surgery

Table 38: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing cardiac surgery?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing cardiac surgery?
Objectives	To find the most effective strategy for preventing VTE in people undergoing cardiac surgery who are admitted to and discharged from hospital
Population	Adults and young people (16 years and older) undergoing cardiac surgery who are : • Admitted to hospital • Outpatients post-discharge
Interventions	Mechanical: • Anti-embolism stockings (AES) (above or below knee) • Intermittent pneumatic compression (IPCD) devices (full leg or below knee) • Foot pumps or foot impulse devices (FID) • Electrical stimulation (including Geko devices) • Continuous passive motion Pharmacological: • Unfractionated heparin (UFH) (low dose, administered subcutaneously) • Low molecular weight heparin (LMWH), licensed in UK: ○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60mg twice daily*) ○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing cardiac surgery?
	patients – maximum 7500 twice units daily*) ○ tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) • LMWH, licensed in countries other than UK: ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) ○ Certoparin (3000 units daily) ○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) ○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) ○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) • Vitamin K Antagonists: ○ warfarin (variable dose only) ○ acenocoumarol (all doses) ○ phenindione (all doses) • Fondaparinux (all doses)* • Apixaban (all doses)* • Dabigatran (all doses)* • Rivaroxaban (all doses)* Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: • Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) • No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Standard versus extended duration prophylaxis. • Low versus high dose for LMWH • Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: • All-cause mortality (up to 90 days from hospital discharge) • Deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) • Pulmonary embolism (up to 90 days from hospital discharge) (NMA outcome). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE • Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing cardiac surgery?
	site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding • Fatal PE (up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. • Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study) • Major adverse cardiac events (MACE) (duration of study): death, Q-wave myocardial infarction (MI) and the need for repeat revascularization by redo-CABG or repeat percutaneous intervention
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	• Primary and community care when continuing prophylaxis after hospital discharge • Secondary care
Exclusions	• Community settings and hospices, except when continuing prophylaxis that has been started in hospital • People who are contraindicated for both mechanical and pharmacological prophylaxis • People with suspected or confirmed venous thromboembolism • Secondary prevention of VTE • Early mobilisation and leg exercises • Non-English studies • Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: • LMWH • Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	• People who are contraindicated for pharmacological prophylaxis • People who are contraindicated for mechanical prophylaxis
Subgroup analyses if there is heterogeneity	• BMI: not obese (BMI under 30kg/m2); obese (BMI over 30kg/m2); severely obese (BMI over 35kg/m2); • Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) • Cardiac bypass • Bowel surgery • Dual antiplatelet therapy; single antiplatelet therapy

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing cardiac surgery?
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness For major bleeding and clinically relevant non-major bleeding outcomes measured at 46 to 90 days will be downgraded for indirectness
Search strategy	Databases: • Medline, Embase, The Cochrane Library Date limits: • Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). • Final search date for CG92: 10 December 2008

C.35 Thoracic surgery

Table 39: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing thoracic surgery?

Objectives	To find the most effective strategy for preventing VTE in people undergoing thoracic surgery who are admitted to and discharged from hospital
Population	Adults and young people (16 years and older) undergoing thoracic surgery who are admitted to hospital, and outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Pharmacological (no minimum duration): Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily)

Objectives	To find the most effective strategy for preventing VTE in people undergoing thoracic surgery who are admitted to and discharged from hospital
	Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose), acenocoumarol (all doses), phenindione (all doses) Fondaparinux (all doses) Apixaban (all doses) Dabigatran (all doses) Rivaroxaban (all doses) Aspirin (up to 300mg)* *off-licence
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge Low versus high dose for LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) (NMA outcome) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) (NMA outcome) Pulmonary embolism (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE (NMA outcome) Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (NMA outcome) Fatal PE (up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy Health-related quality of life (validated scores only)(up to 90 days from hospital

Objectives	To find the most effective strategy for preventing VTE in people undergoing thoracic surgery who are admitted to and discharged from hospital
	discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Studies where people received or were assumed to have received treatment for their conditions that is not used in current practice Thoracic surgery Bariatric surgery People with suspected or confirmed venous thromboembolism Community settings and hospices, except when continuing prophylaxis that has been started in hospital Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of study <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together Outcomes reported pre- and post-operative discharge will be analysed together GRADE assessments will be conducted. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness. For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Stratification	People who are contraindicated for pharmacological prophylaxis People who are contraindicated for mechanical prophylaxis
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2) obese (obesity I and II, 30–34.9kg/m2); severely obese (obesity III, ≥40kg/m2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer Surgery type: Thoracoscopic; open thoracic
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.36 Vascular surgery

Table 40: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing vascular surgery?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing vascular surgery?
Objectives	To find the most effective strategy for preventing VTE in people undergoing vascular surgery who are admitted to and discharged from hospital
Population	Adults and young people (16 years and older) undergoing cardiac surgery who are : Admitted to hospital Discharged from hospital Outpatients
Interventions	Mechanical: Anti-embolism stockings (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Vena caval filters Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)*

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing vascular surgery?
	Aspirin (up to 300mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis. Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Community settings and hospices, except when continuing prophylaxis that has been started in hospital People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing vascular surgery?
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated Varicose veins Lower limb amputation Open vascular surgery (major aortic/leg bypass)
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30kg/m2); obese (BMI over 30kg/m2); severely obese (BMI over 35kg/m2); Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30) Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer Open; endovascular aortic/iliac; not aortic/iliac
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness For major bleeding and clinically relevant non-major bleeding outcomes measured at 46 to 90 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.37 Head and neck surgery

C.37.1 Oral and maxillofacial surgery

Table 41: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing oral or maxillofacial surgery?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing oral or maxillofacial surgery?
Objectives	To find the most effective strategy for preventing VTE in people undergoing oral or maxillofacial surgery who are admitted to and discharged from hospital, and people having day procedures
Population	Adults and young people (16 years and older) undergoing oral or maxillofacial surgery who are:

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing oral or maxillofacial surgery?
	Admitted to hospital Having day procedures Outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300 mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing oral or maxillofacial surgery?
	Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7–90 days from hospital discharge) (NMA outcome). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7–90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2 g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7–90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study) Cerebral sinus thrombosis (30 days)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	Dental surgery People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Community settings and hospices, except when continuing prophylaxis that has been started in hospital Early mobilisation and leg exercises Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing oral or maxillofacial surgery?
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30 kg/m^2) obese (obesity I and II, 30–34.9 kg/m^2); severely obese (obesity III, ≥40 kg/m^2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30)
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

C.37.2 Ear, nose and throat (ENT) surgery

Table 42: Review protocol: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing ear, nose or throat (ENT) surgery?

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing ear, nose or throat (ENT) surgery?
Objectives	To find the most effective strategy for preventing VTE in people undergoing ear, nose or throat (ENT) surgery who are admitted to and discharged from hospital, and having day procedures
Population	Adults and young people (16 years and older) undergoing ear, nose or throat (ENT) who are: Admitted to hospital Having day procedures Outpatients post-discharge
Interventions	Mechanical: Anti-embolism stockings (AES) (above or below knee) Intermittent pneumatic compression (IPCD) devices (full leg or below knee) Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Vena caval filters Pharmacological: Unfractionated heparin (UFH) (low dose, administered subcutaneously) Low molecular weight heparin (LMWH), licensed in UK: enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*) dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing ear, nose or throat (ENT) surgery?
	daily*) tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) LMWH, licensed in countries other than UK: Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) Certoparin (3000 units daily) Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) Vitamin K Antagonists: warfarin (variable dose only) acenocoumarol (all doses) phenindione (all doses) Fondaparinux (all doses)* Apixaban (all doses)* Dabigatran (all doses)* Rivaroxaban (all doses)* Aspirin (up to 300 mg)* *off-label
Comparisons	Compared to: Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: Above versus below knee stockings Full leg versus below knee IPC devices Standard versus extended duration prophylaxis Low versus high dose for LMWH Preoperative versus post-operative initiation of LMWH
Outcomes	Critical outcomes: All-cause mortality (up to 90 days from hospital discharge) Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) Pulmonary embolism (7-90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding Fatal PE (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy;

Review question	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing ear, nose or throat (ENT) surgery?
	echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study) Cerebral sinus thrombosis
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.
Settings	Primary and community care when continuing prophylaxis after hospital discharge Secondary care
Exclusions	People undergoing diagnostic tests only People who are contraindicated for both mechanical and pharmacological prophylaxis People with suspected or confirmed venous thromboembolism Secondary prevention of VTE Early mobilisation and leg exercises Community settings and hospices, except when continuing prophylaxis that has been started in hospital Non-English studies Duration of follow-up <7 days; >150 days
Review strategy	Drug groups combined for analysis: LMWH Vitamin K Antagonists Outcomes reported at different time points will be analysed together
Stratification	People who are contraindicated Active cancer (defined as receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma); no active cancer Diagnostic and endoscopic surgery
Subgroup analyses if there is heterogeneity	BMI: not obese (BMI under 30 kg/m^2) obese (obesity I and II, 30–34.9 kg/m^2); severely obese (obesity III, ≥40 kg/m^2) Renal impairment (no renal impairment eGFR >30; renal impairment eGFR <30)
Other analysis	The quality of the data will be assessed using GRADE. Outcomes that are not confirmed by methods listed in protocol, or where methods of confirmation are not reported, will be downgraded for indirectness For all-cause mortality, DVT, PE, fatal PE, quality of life and heparin-induced thrombocytopenia outcomes measured at 91 to 150 days will be downgraded for indirectness
Search strategy	Databases: Medline, Embase, The Cochrane Library Date limits: Update of previous NICE guideline: Venous thromboembolism - reducing the risk (CG92). Final search date for CG92: 10 December 2008

Review question	**What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing ear, nose or throat (ENT) surgery?**

Appendix D: Health economic review protocol

Table 43: Health economic review protocol

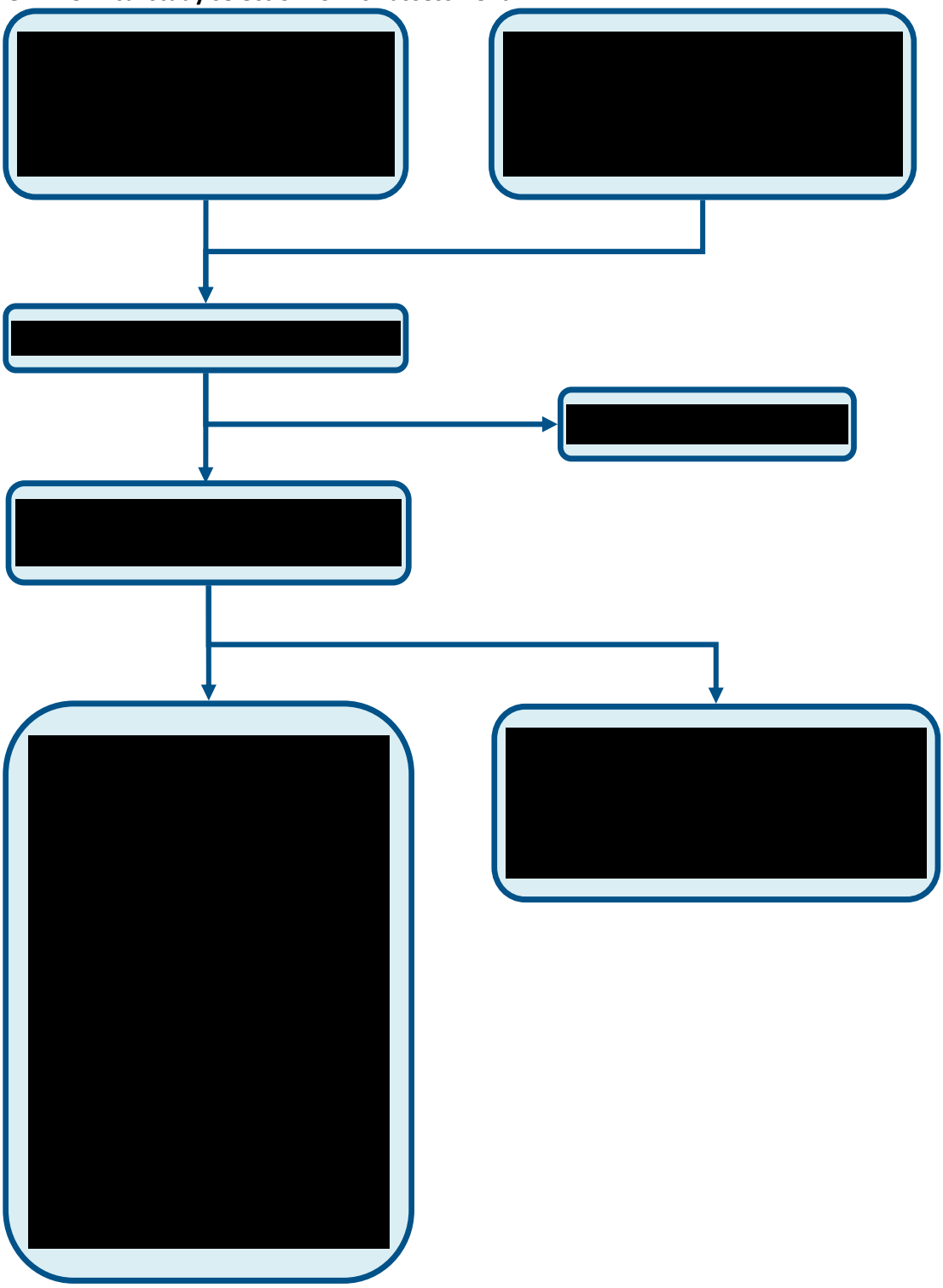
Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G. For questions being updated from the previous guidelines, the search will be run from the latest guideline (CG92) cut-off date (2008).
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001 will be excluded. Abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2001 that were included in the previous guidelines will be re-assessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix H of Developing NICE guidelines: the manual (2014).[236] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the Committee if required. The ultimate aim is to include economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the Committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix O.

	The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* • Cost-utility analysis (most applicable). • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in [2001] or later that were included in the previous guidelines but that depend on unit costs and resource data entirely or predominantly from before [2001] will be rated as 'Not applicable'. • Studies published before [2001] will be excluded. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the clinical effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix E: Clinical study selection

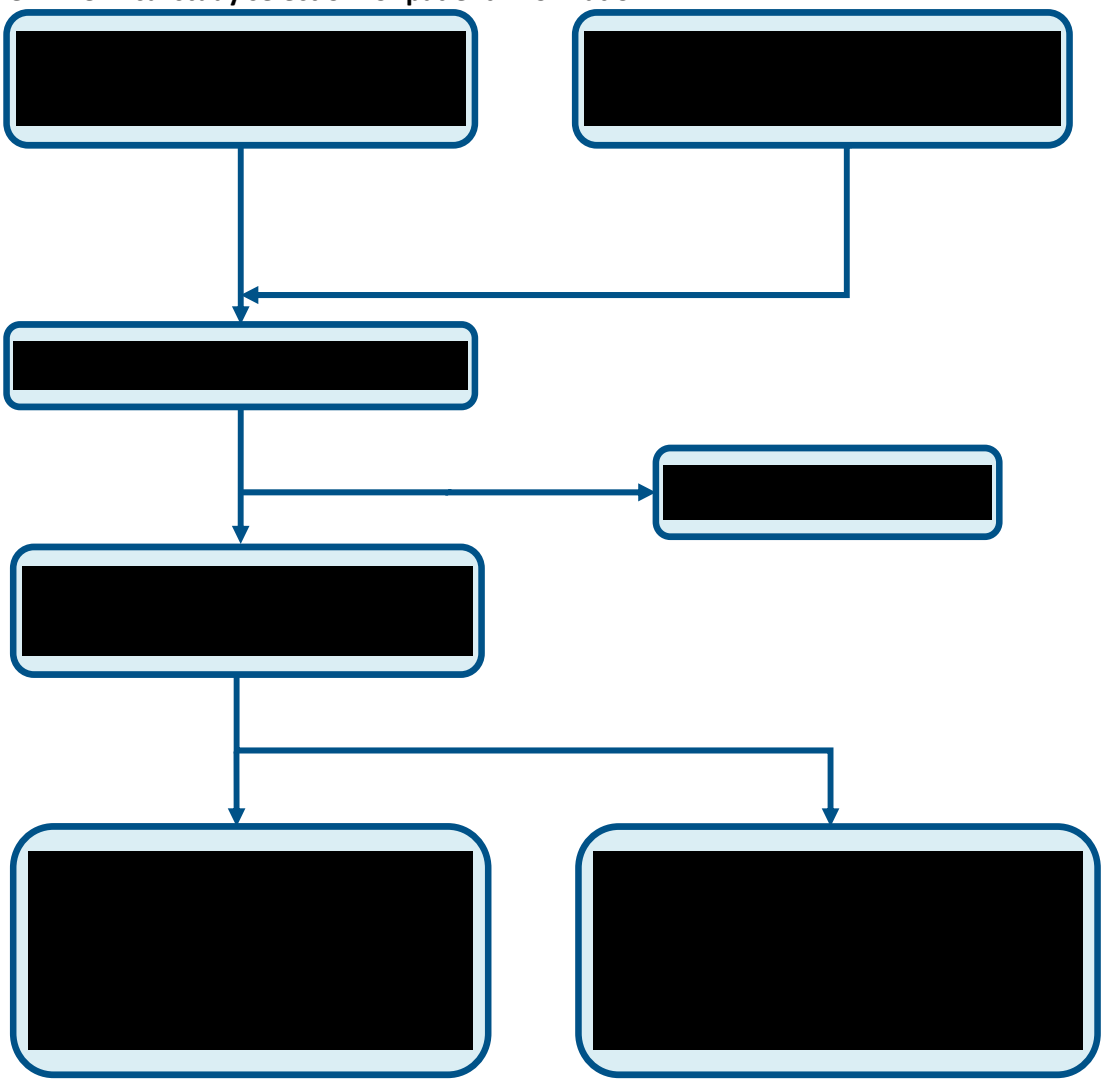
E.1 Risk assessment

Figure 1: Clinical study selection for risk assessment



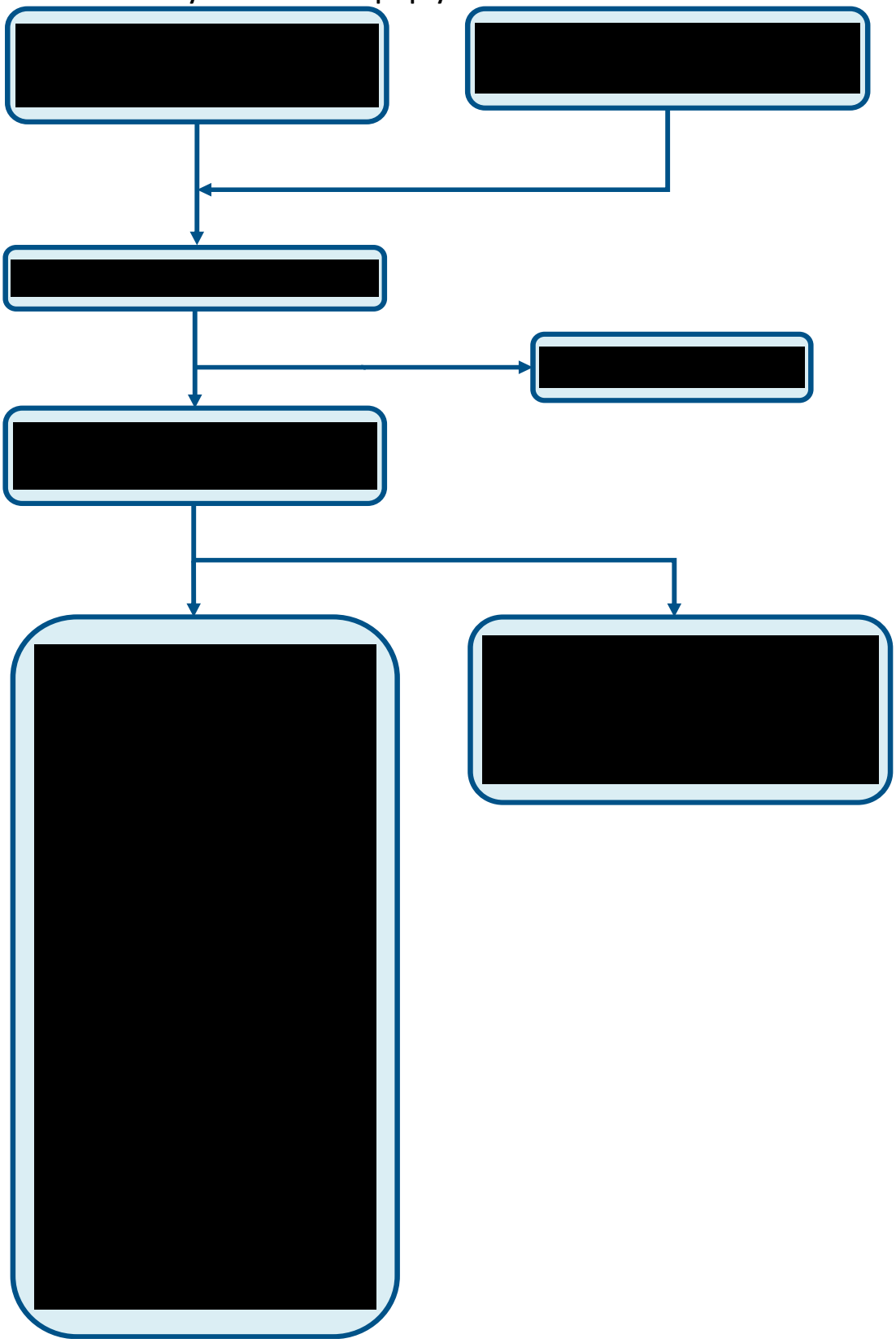
E.2 Patient information

Figure 2: Clinical study selection for patient information



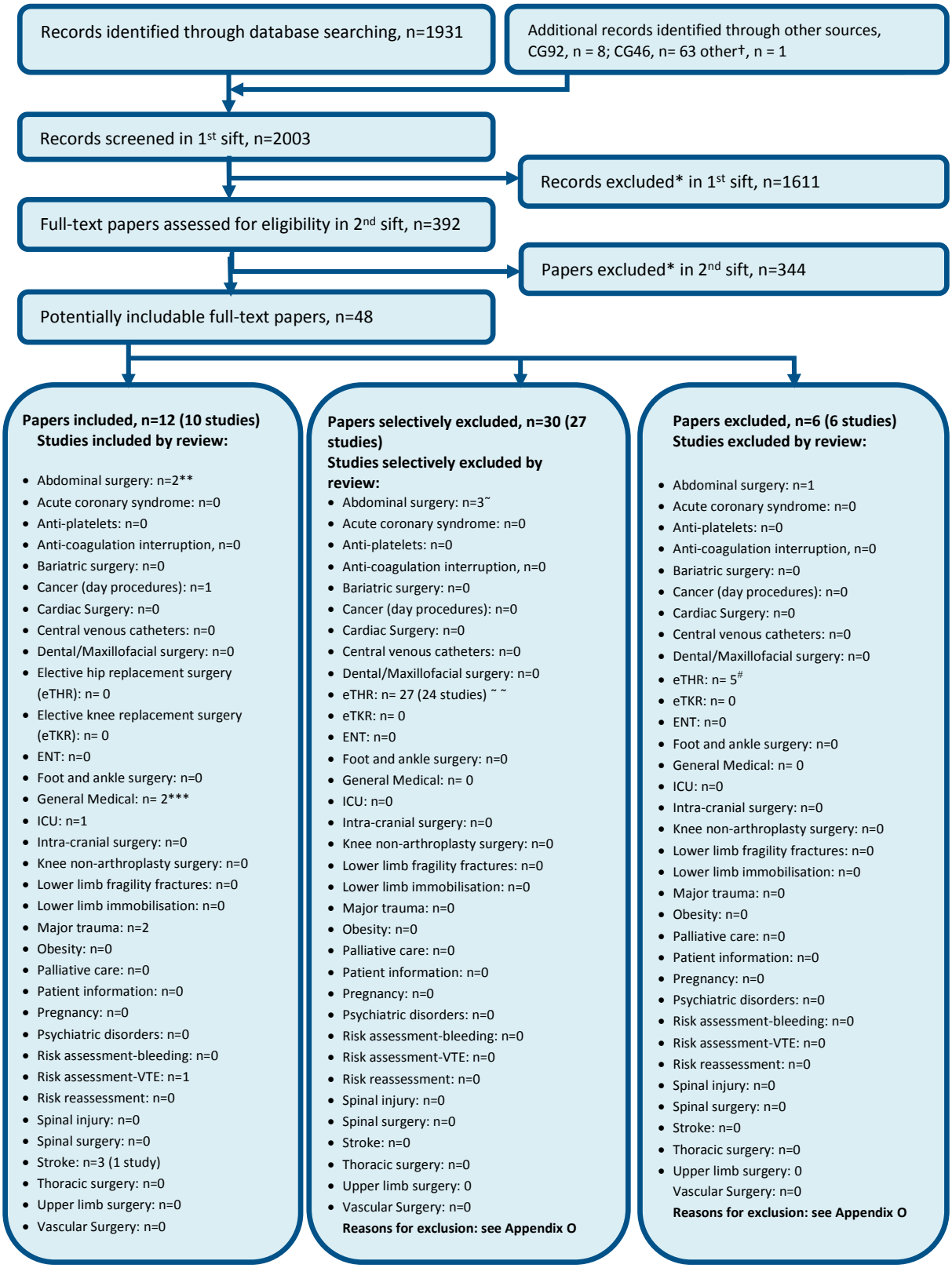
E.3 VTE prophylaxis

Figure 3: Clinical study selection for VTE prophylaxis



Appendix F: Health economic study selection

Figure 4: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language; † Author contact. ** One article identified was applicable to eTHR, eTKR, bariatric, thoracic and abdominal surgery. It has been included under abdominal surgery only and selectively excluded for eTHR and eTKR. CG92 models covered 4 populations: abdominal surgery, eTHR, eTKR and general medical. It has been included under "abdominal surgery" only. *** One article identified was applicable to general medical and risk assessment-VTE, for the purposes of this diagram it has been included under the first only. ~ two articles identified were applicable to abdominal surgery, eTHR and eTKR. It has been included under abdominal surgery only. ~ ~Twenty-two articles identified were applicable to eTHR and eTKR. These have been included under eTHR only. # All 5 articles were applicable to eTHR and eTKR. Two were applicable to eTHR, eTKR and lower limb fragility fracture. These have been included only under eTHR.

Appendix G: Literature search strategies

G.1 Contents

Introduction	**Search methodology**
Section G.2	**Population search strategy**
G.2.1	Standard venous thromboembolism population This population was used for all search questions unless stated
Section G.3	**Study filter search terms**
G.3.1	Excluded study designs and publication types
G.3.2	Randomised controlled trials (RCT)
G.3.3	Systematic reviews (SR)
G.3.4	Health economic studies (HE)
G.3.5	Quality of life studies (QoL)
G.3.6	Qualitative reviews (QUAL)
Section G.4	**Searches for specific questions with intervention**
G.4.1	Risk assessment
G.4.2	Provision of information to patients and planning for discharge
G.4.3	General VTE prevention for all populations
Section G.5	**Health economics search terms**
G.5.1	Health economic reviews
G.5.2	Quality of life reviews

Search strategies used for the venous thromboembolism (VTE) guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual 2014, updated 2017 available from https://www.nice.org.uk/article/pmg20/. All searches were run up to 19 June 2017 unless otherwise stated. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text. Where possible searches were limited to retrieve material published in English.

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Additional searches were run in CINAHL, Current Nursing and Allied Health Literature (EBSCO) and PsycINFO (ProQuest), see Table 44.

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

Searches for **patient views** were run in Medline, Embase, CINAHL and PsycINFO. Searches were constructed by adding a patient views search filter to the population terms.

Table 44: Databases searched

Question	Question number	Databases
General VTE prevention for all populations	G.4.3	Medline, Embase and Cochrane Library
Provision of information to patients and	G.4.2	Medline, Embase, CINAHL and

Question	Question number	Databases
planning for discharge		PsycINFO
Risk assessment	G.4.1	Medline, Embase and Cochrane Library

Searches for **health economic reviews** were run in Medline, Embase, the NHS Economic Evaluations Database (NHS EED) and the Health Technology Assessment (HTA). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD).

For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy. Searches in CRD were constructed using population terms only.

G.2 Population search strategies

G.2.1 Standard venous thromboembolism (VTE) population

Medline search terms

1.	pulmonary embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or upper extremity deep vein thrombosis/
2.	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj3 (embolism or emboli or embolus or emboliz* or thromboembolism))).ti,ab.
3.	1 or 2

Embase search terms

1.	thromboembolism/ or venous thromboembolism/ or vein thrombosis/ or deep vein thrombosis/ or leg thrombosis/ or lower extremity deep vein thrombosis/ or postoperative thrombosis/ or lung embolism/ or upper extremity deep vein thrombosis/
2.	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj3 (embolism or emboli or embolus or emboliz* or thromboembolism))).ti,ab.
3.	1 or 2

Cochrane search terms

#1.	MeSH descriptor: [venous thromboembolism] this term only
#2.	MeSH descriptor: [pulmonary embolism] this term only
#3.	MeSH descriptor: [venous thrombosis] this term only
#4.	MeSH descriptor: [thromboembolism] this term only
#5.	MeSH descriptor: [upper extremity deep vein thrombosis] this term only
#6.	((*venous or *vein) next (thrombosis or thromboses or thrombus or thromboembolism) or dvt or vte or (pulmonary or lung) near/3 (embolism or emboli or embolus or emboliz* or thromboembolism)):ti,ab
#7.	#1 or #2 or #3 or #4 or #6

CINAHL search terms

S1.	(mh "pulmonary embolism") or (mh "venous thrombosis") or (mh "venous thromboembolism") or (mh "thromboembolism")
S2.	(((venous or vein) n1 (thrombosis or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) n3 (embolism or emboli or embolus or thromboembolism)))
S3.	s1 or s2

PsycINFO search terms

1.	su.exact.explode("embolisms") or su.exact.explode("thromboses") or ti,ab((venous or vein) n/1 (thrombosis or thromboses or thrombus or thromboembolism)) or ti,ab(dvt or vte) or ti,ab((pulmonary or lung) n/3 (embolism or emboli or embolus or emboliz* or thromboembolism))

CRD search terms

#1.	MeSH descriptor venous thromboembolism explode all trees
#2.	MeSH descriptor pulmonary embolism explode all trees
#3.	MeSH descriptor venous thrombosis explode all trees
#4.	MeSH descriptor thromboembolism explode all trees
#5.	MeSH descriptor upper extremity deep vein thrombosis explode all trees
#6.	(dvt)
#7.	(vte)
#8.	(((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism)))
#9.	((pulmonary or lung) adj3 (embolism or emboli or embolus or emboliz* or thromboembolism))
#10.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

G.3 Study filter search terms

G.3.1 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator:

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.

4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

G.3.2 Randomised controlled trials (RCT)

Medline search terms

(Based on the sensitivity and precision maximising version reported in the Cochrane Handbook (http://handbook.cochrane.org/)).

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ti,ab.
4.	placebo.ab.
5.	randomly.ab.
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

G.3.3 Systematic reviews (SR)

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.

4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

G.3.4 Health economic studies (HE)

Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

Embase search terms

1.	health economics/
2.	exp economic evaluation/

3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

G.3.5 Quality of life studies (QoL)

Medline search terms

1.	quality-adjusted life years/
2.	sickness impact profile/
3.	(quality adj2 (wellbeing or well-being)).ti,ab.
4.	sickness impact profile.ti,ab.
5.	disability adjusted life.ti,ab.
6.	(qal* or qtime* or qwb* or daly*).ti,ab.
7.	(euroqol* or eq5d* or eq 5d*).ti,ab.
8.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9.	(health utility* or utility score* or disutilit*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).ti,ab.
13.	rosser.ti,ab.
14.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
19.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
20.	or/1-19

Embase search terms

1.	quality adjusted life year/
2.	"quality of life index"/
3.	short form 12/ or short form 20/ or short form 36/ or short form 8/
4.	sickness impact profile/
5.	(quality adj2 (wellbeing or well-being)).ti,ab.
6.	sickness impact profile.ti,ab.
7.	disability adjusted life.ti,ab.

8.	(qal* or qtime* or qwb* or daly*).ti,ab.
9.	(euroqol* or eq5d* or eq 5d*).ti,ab.
10.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11.	(health utility* or utility score* or disutilit*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).ti,ab.
15.	rosser.ti,ab.
16.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
18.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
20.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
21.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
22.	or/1-21

G.3.6 Qualitative reviews (QUAL)

Medline search terms

1.	qualitative research/ or narration/ or exp interviews as topic/ or exp questionnaires/ or health care surveys/
2.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
3.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
4.	or/1-3

Embase search terms

1.	health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/
2.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
3.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
4.	or/1-3

CINAHL search terms

S1.	(mh "qualitative studies+")
S2.	(mh "qualitative validity+")
S3.	(mh "interviews+") or (mh "focus groups") or (mh "surveys") or (mh "questionnaires+")
S4.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*)
S5.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)
S6.	S1 or s2 or S3 or S4 or S5

G.4 Searches for specific questions

G.4.1 Risk Assessment

- What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE in patients?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	(risk* adj2 assess*).ti,ab.
6.	((score* or scoring) adj2 (tool* or system*)).ti,ab.
7.	((risk* or predict* or prognos*) adj4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)).ti,ab.
8.	(vienna adj5 cats).ti,ab.
9.	(vienna cancer and thrombosis study).ti,ab.
10.	trauma embolic scoring.ti,ab.
11.	tess.ti,ab.
12.	(roger* or caprini* or kucher* or cohen* or padua* or khorana* or autar).ti,ab.
13.	(well* adj2 (score* or scoring)).ti,ab.
14.	department of health.ti,ab,au.
15.	or/5-14
16.	4 and 15
	Date parameters: 1946 – 19 June 2017

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	(risk* adj2 assess*).ti,ab.
6.	((score* or scoring) adj2 (tool* or system*)).ti,ab.
7.	((risk* or predict* or prognos*) adj4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)).ti,ab.
8.	(vienna adj5 cats).ti,ab.
9.	(vienna cancer and thrombosis study).ti,ab.
10.	trauma embolic scoring.ti,ab.
11.	tess.ti,ab.
12.	(roger* or caprini* or kucher* or cohen* or padua* or khorana* or autar).ti,ab.
13.	(well* adj2 (score* or scoring)).ti,ab.
14.	department of health.ti,ab,au.
15.	or/5-14
16.	4 and 15
	Date parameters: 1974 – 19 June 2017

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	(risk* near/2 assess*):ti,ab
#3.	((score* or scoring) near/2 (tool* or system*)):ti,ab
#4.	((risk* or predict* or prognos*) near/4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)):ti,ab
#5.	(vienna near/5 cats):ti,ab
#6.	(vienna cancer and thrombosis study):ti,ab
#7.	trauma embolic scoring:ti,ab
#8.	tess:ti,ab
#9.	(roger* or caprini* or kucher* or cohen* or padua* or khorana* or autar):ti,ab
#10.	(well* near/2 (score* or scoring)):ti,ab
#11.	(department of health):ti,ab
#12.	(or #2-#11)
#13.	#1 and #12
	Inception – 19 June 2017

G.4.2 Provision of information to patients and planning for discharge

- What information about VTE and VTE prophylaxis should be given to people who are admitted to hospital, having day procedures or outpatients post-discharge, and their family or carers?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	"patient acceptance of health care"/ or exp patient satisfaction/
6.	patient education as topic/
7.	((information* or advice or advising or advised or support*) adj3 (patient* or need* or requirement* or assess* or seek* or access* or disseminat*)).ti,ab.
8.	(information* adj2 support*).ti,ab.
9.	((client* or patient* or user* or carer* or consumer* or customer*) adj2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)).ti,ab.
10.	or/5-9
11.	Study filter QUAL (G.3.6)
12.	4 and 10 and 11
	Date parameters: 2008-19 June 2017

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	patient attitude/ or patient preference/ or patient satisfaction/ or consumer attitude/
6.	patient information/ or consumer health information/
7.	patient education/
8.	((information* or advice or advising or advised or support*) adj3 (patient* or need* or requirement* or assess* or seek* or access* or disseminat*)).ti,ab.

9.	(information* adj2 support*).ti,ab.
10.	((client* or patient* or user* or carer* or consumer* or customer*) adj2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)).ti,ab.
11.	or/5-10
12.	Study filter QUAL (G.3.6)
13.	4 and 11 and 12
	Date parameters: 2008-19 June 2017

PsycINFO search terms

1.	Standard population [G.2.1]
2.	su.exact("client education") or su.exact.explode("client attitudes") or ti,ab((information* or advice or advising or advised or support*) n/3 (patient* or need* or requirement* or assess* or seek* or access* or disseminat*)) or ti,ab(information* n/2 support*) or ti,ab((client* or patient* or user* or carer* or consumer* or customer*) n/2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*))
3.	Study filter QUAL (G.3.6)
4.	1 and 2 and 3
	Date parameters: 2008-19 June 2017

Cinahl search terms

S1.	Standard population [G.2.1]
S2.	Limit 1 to English language
S3.	(MH "consumer satisfaction+") OR (MH "patient education") OR (MH "health education")
S4.	((information* or advice or advising or advised or support*) n3 (patient* or need* or requirement* or assess* or seek* or access* or disseminat*))
S5.	(information* n2 support*)
S6.	((client* or patient* or user* or carer* or consumer* or customer*) n2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*))
S7.	S3 or S4 or S5 or S6
S8.	S2 and S7
	Date parameters: 2008-19 June 2017

G.4.3 General VTE prevention for all populations

- What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination)?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	exp anticoagulants/
6.	exp fibrinolytic agents/
7.	(anticoagula* or anti coagula* or antithromb* or anti thromb* or antiemboli* or anti emboli* or thrombin inhibit* or direct thrombin).ti,ab.
8.	(dabigatran or pradaxa or danaparoid or orgaran).ti,ab.
9.	exp heparin/

10.	(heparin or lmwh).ti,ab.
11.	(calciparine or monoparin or calcium multiparin or bemiparin or zibor or dalteparin or fragmin* or enoxaparin or clexane or lovenox or tinzaparin or innohep or antixarin or cy 222 or embolex or monoembolex or tinzaparin or suleparoid* or ardeparin or certoparin or nadroparin or parnaparin or reviparin or tedelparin* or minolteparin or semuloparin).ti,ab.
12.	acenocoumarol/ or warfarin/
13.	phenindione/
14.	(warfarin or marevan or acenocoumarol or nicoumalone or sinthrome or phenindione).ti,ab.
15.	(apixaban or eliquis or rivaroxaban or xarelto or edoxaban or lixiana or savaysa or fondaparinux or arixtra).ti,ab.
16.	aspirin/
17.	(aspirin or acetylsalicylic acid).ti,ab.
18.	stockings, compression/
19.	(stocking or stockings or hose).ti,ab.
20.	intermittent pneumatic compression devices/
21.	((inflat* or pneumat*) adj2 (jacket* or sleeve* or glove* or boot*)).ti,ab.
22.	(((calf or elastic or graded or limb or leg or pneumatic or plantar or foot) adj compression) or (compression adj device)).ti,ab.
23.	((foot or feet) adj2 (pump or pumps or device*)).ti,ab.
24.	flowtron.ti,ab.
25.	motion therapy, continuous passive/
26.	(therap* adj3 (cpm or continuous passive)).ti,ab.
27.	electric stimulation/
28.	((electric* or electro*) adj2 stimulat*).ti,ab.
29.	or/5-28
30.	Study filters RCT (G.3.2) or SR (G.3.3)
31.	4 and 29 and 30
	Date parameters: 2008-19 June 2017

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	exp anticoagulant agent/
6.	exp fibrinolytic agent/
7.	(anticoagula* or anti coagula* or antithromb* or anti thromb* or antiemboli* or anti emboli* or thrombin inhibit* or direct thrombin).ti,ab.
8.	dabigatran/ or dabigatran etexilate/
9.	danaparoid/
10.	(dabigatran or pradaxa or danaparoid or orgaran).ti,ab.
11.	heparin/
12.	low molecular weight heparin/
13.	dalteparin/ or enoxaparin/ or nadroparin/ or heparinoid/
14.	(heparin or lmwh).ti,ab.
15.	(calciparine or monoparin or calcium multiparin or bemiparin or zibor or dalteparin or fragmin* or enoxaparin or clexane or lovenox or tinzaparin or innohep or antixarin or cy 222 or embolex or monoembolex or fragmin or tinzaparin or suleparoid* or ardeparin or certoparin

	or nadroparin or parnaparin or reviparin or tedelparin).ti,ab.
16.	acenocoumarol/ or warfarin/ or phenindione/
17.	(warfarin or marevan or acenocoumarol or nicoumalone or sinthrome or phenindione).ti,ab.
18.	apixaban/ or rivaroxaban/ or edoxaban/ or fondaparinux/
19.	(apixaban or eliquis or rivaroxaban or xarelto or edoxaban or lixiana or savaysa or fondaparinux or arixtra).ti,ab.
20.	acetylsalicylic acid/
21.	(aspirin or acetylsalicylic acid).ti,ab.
22.	compression stocking/
23.	(stocking or stockings or hose).ti,ab.
24.	intermittent pneumatic compression device/
25.	((inflat* or pneumat*) adj2 (jacket* or sleeve* or glove* or boot*)).ti,ab.
26.	(((calf or elastic or graded or limb or leg or pneumatic or plantar or foot) adj compression) or (compression adj device)).ti,ab.
27.	((foot or feet) adj2 (pump or pumps or device*)).ti,ab.
28.	flowtron.ti,ab.
29.	passive movement/
30.	(therap* adj3 (cpm or continuous passive)).ti,ab.
31.	electrostimulation/
32.	((electric* or electro*) adj2 stimulat*).ti,ab.
33.	or/5-32
34.	Study filters RCT (G.3.2) or SR (G.3.3)
35.	4 and 33 and 34
	Date parameters: 2008-19 June 2017

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	MeSH descriptor: [anticoagulants] explode all trees
#3.	MeSH descriptor: [fibrinolytic agents] explode all trees
#4.	(anticoagula* or anti coagula* or antithromb* or anti thromb* or antiemboli* or anti emboli* or thrombin inhibit* or direct thrombin):ti,ab
#5.	(dabigatran or pradaxa or danaparoid or orgaran):ti,ab
#6.	MeSH descriptor: [heparin] explode all trees
#7.	(heparin or lmwh):ti,ab
#8.	(calciparine or monoparin or calcium multiparin or bemiparin or zibor or dalteparin or fragmin* or enoxaparin or clexane or lovenox or tinzaparin or innohep or antixarin or cy 222 or embolex or monoembolex or fragmin or tinzaparin or suleparoid* or ardeparin or certoparin or nadroparin or parnaparin or reviparin or tedelparin):ti,ab
#9.	MeSH descriptor: [acenocoumarol] explode all trees
#10.	MeSH descriptor: [warfarin] explode all trees
#11.	MeSH descriptor: [phenindione] explode all trees
#12.	(warfarin or marevan or acenocoumarol or nicoumalone or sinthrome or phenindione):ti,ab
#13.	(apixaban or eliquis or rivaroxaban or xarelto or edoxaban or lixiana or savaysa or fondaparinux or arixtra):ti,ab
#14.	MeSH descriptor: [aspirin] explode all trees
#15.	(aspirin or acetylsalicylic acid):ti,ab
#16.	MeSH descriptor: [stockings, compression] explode all trees
#17.	(stocking or stockings or hose):ti,ab

#18.	MeSH descriptor: [intermittent pneumatic compression devices] explode all trees
#19.	((inflat* or pneumat*) near/2 (jacket* or sleeve* or glove* or boot*)):ti,ab
#20.	(((calf or elastic or graded or limb or leg or pneumatic or plantar or foot) near/1 compression) or (compression near/1 device)):ti,ab
#21.	((foot or feet) near/2 (pump or pumps or device*)):ti,ab
#22.	flowtron.ti,ab
#23.	MeSH descriptor: [motion therapy, continuous passive] explode all trees
#24.	(therap* near/3 (cpm or continuous passive)):ti,ab
#25.	MeSH descriptor: [electric stimulation] explode all trees
#26.	((electric* or electro*) near/2 stimulat*):ti,ab
#27.	(or #2-#26)
#28.	#1 and #27
	Date parameters: 2008-19 June 2017

G.5 Health economics search terms

Economic searches were conducted in Medline, Embase and NHS EED and HTA databases hosted by CRD.

G.5.1 Health economic (HE) reviews

Economic searches were conducted in Medline, Embase, Cochrane and CRD.

Medline & Embase search terms

1.	#29.	Standard population [G.2.1]
2.	#30.	Excluded study designs and publication types [G.3.1]
3.	#31.	1 not 2
4.	#32.	Limit 3 to English language
5.	#33.	Study filter HE (G.3.4)
6.	#34.	4 and 5
#35.	#36.	Date parameters: 2013-19 June 2017

Cochrane search terms

#1.	Standard population [G.2.1]
	Date parameters: 2008-19 June 2017

CRD search terms

#1.	Standard population [G.2.1]
	Date parameters: 1999 - 2008

G.5.2 Quality of life (QoL) reviews

Quality of life searches were conducted in Medline and Embase only

Medline & Embase search terms

1.	#37.	Standard population [G.2.1]
2.	#38.	Excluded study designs and publication types [G.3.1]
3.	#39.	1 not 2

4.	#40.	Limit 3 to English language
5.	#41.	Study filter QOL (G.3.5)
6.	#42.	4 and 5
#43.	#44.	Date parameters: 2008-19 June 2017

Appendix H: Clinical evidence tables

H.1 Risk assessment for people admitted to hospital

H.1.1 Patients admitted to hospital

Reference	Bahl 2010 [12]
Study type	Retrospective cohort
Study methodology	Data source: general, vascular and urologic surgery inpatients from the University of Michigan Health System (UMHS) National Surgical Quality Improvement (NSQIP) program discharged between July 2001 and January 2008. Data for VTE risk factor were obtained from electronic sources. Validation: external validation.
Number of patients	n=8216
Patient characteristics	Age: <40 years 19.28%, 40-60 years 39.59%, 61-74 years 28.4%, 75+ years 12.73% Gender (male to female ratio): not reported Ethnicity: not reported Condition(s): acute myocardial infarction 0.22%; heart failure 3.93%; varicose veins 0.11%; obesity (BMI >25) 24.71%; inflammatory bowel disease 2.98%; sepsis (<1 month) 0.85%; COPD or abnormal pulmonary function 7.57%; severe lung disease, including pneumonia (<1 month) 0.68%; pregnancy or postpartum (<1 month) 0.19%; malignancy (present or previous) 34.98%; Surgery: major surgery (>45 minutes) 88.16%; general 67%, vascular 16%, 17% urologic; minor surgery planned 5.66%; arthroscopic surgery 0%; laparoscopic procedure (>45 minutes) 6.18%; history of DVT/PE 3.47%; stroke (<1 month) 0.15%; multiple trauma (<1 month) 0.04% Other relevant characteristics: central venous access 7.64%; elective major lower extremity arthroplasty 0.01%; hip, pelvis or leg fracture 0%; acute spinal cord injury (paralysis) 0% Setting: hospital Country: USA

Reference	Bahl 2010 [12]
	Inclusion criteria: general, vascular and urologic surgery inpatients from the University of Michigan Health System (UMHS) National Surgical Quality Improvement (NSQIP) program discharged between July 2001 and January 2008 Exclusion criteria: none stated
Target condition(s)	VTE (30 days): not defined. Prevalence: n= 188 (1.44%)
Risk tool(s)	Caprini score Total score is used to place people in one of three main risk categories: low (scores 0-4), moderate (5-8) and high (≥9). Includes 25 predictors. Score 1: • Age 40-59 (years) • Abnormal pulmonary function • Acute myocardial infarction (<1 month) • BMI ≥30 (kg/m2) • Congestive heart failure (<1 month) • History of inflammatory bowel disease • History of prior major surgery (<1 month) • Complications of pregnancy (history of unexplained stillborn infant, recurrent or spontaneous abortion (>3), premature birth with toxemia of pregnancy, or growth-restricted infant) • Oral contraceptive use or hormone replacement therapy (HRT) • Sepsis (<1 month) • Serious acute lung disease (<1 month) • Swollen legs (current) • Varicose veins Score 2: • Age 60-74 (years) • Central venous access • Confined to bed (>72 hours) • Major open surgery (≥45 minutes) • Present cancer • Prior cancer, except non-melanoma skin Score 3: • Age ≥75 (years)

Reference	Bahl 2010 [12]
	• History of VTE • Family history of VTE • Chemotherapy • Positive anticardiolipin antibody • Positive Lupus anticoagulant • Acute spinal cord injury (<1 month) • Major surgery (≥6 hours)
Statistical measures	Caprini score • C-statistic 0.698 (no variance data reported) • Hosmer and Lemeshow test p=0.607
Source of funding	Not reported
Limitations	Patient selection: Unclear if patients were enrolled at a similar state of health Outcome: No VTE definition reported Analysis: Not all relevant performance measures evaluated Sample size and participants: There was not a reasonable number of outcome events
Comments	

Reference	Bilimoria 2013 [30]
Study type	Retrospective cohort
Study methodology	Data source: American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). Data collected by trained and audited Surgical Clinical Reviewers (SCR) at each individual hospital using data definitions which are standardized across all hospitals. Thirty-day outcomes are ascertained from the medical record or patients are contacted after discharge. Outcomes are ascertained irrespective of whether the patient was an inpatient, outpatient, or admitted to another facility. Patients were identified who underwent operations from 1 January 2009 to 30 June 2012, spanning all surgical subspecialties. From the overall dataset, 88,334 cases were identified as colon operations based on primary Current Procedural Terminology (CPT) codes Derivation: Universal ACS NSQIP Surgical Risk Calculator - Preoperative risk factors to be used in calculating patient-specific risks of surgical events were selected a priori based on predictive value, routine availability to the surgeon prior to the operation, and clinical face validity. Missing data were handled with imputation using the Buck's method per the standard ACS NSQIP modelling approach. In prior procedure-specific risk calculators, the operations were grouped into surgery subtypes based on CPT codes (6 groups for colectomy) and into surgical

Reference	Bilimoria 2013 [30]
	indication categories based on International Classification of Disease (ICD-9) codes (8 groups for colectomy). For the universal Surgical Risk Calculator model, a CPT-specific linear risk (different for each outcome) replaced CPT procedure categories in the procedure-specific model, and the universal model did not include an indication variable. The individual CPT-specific linear risks were logit transformed predicted probabilities, from preliminary models where CPT (2,805 different CPTs), as a random effect in a hierarchical model, was used to predict each outcome. Random intercept, fixed slope hierarchical models (using SAS GLIMMIX), which account for clustering of cases within hospitals and impose an empirical-Bayes type shrinkage adjustment, were used. Only fixed (patient-level) effects were used for risk prediction. Validation: Universal ACS NSQIP Surgical Risk Calculator: externally validated, split sample by year ACS NSQIP Colorectal Risk Calculator: externally validated, split sample by year [64]
Number of patients	All surgery n= 1,414,006 (derivation) Colon surgery n= 88,334 (validation)
Patient characteristics	Age: not reported Gender (male to female ratio): 42.7:57.3 Ethnicity: not reported Condition(s): disseminated cancer 2%; diabetes 15.2%; hypertension requiring medication 46.6%; congestive heart failure 30 days before surgery 0.9%; history of severe COPD 4.8%; acute renal failure 0.5% Surgery: colectomy Systemic sepsis with 48 hours before surgery: systemic inflammatory response syndrome (SIRS) 3.9%, sepsis 2.4%, septic shock 0.6% Previous cardiac event: 7.4% Functional status: independent 95.1%, partially dependent 3.7%, totally dependent 1.2% Ventilator dependent: 0.7% Dialysis: 1.6% Current smoker 19.3% Setting: 393 hospitals Country: USA Inclusion criteria: Universal ACS NSQIP Surgical Risk Calculator – people undergoing any operation; ACS NSQIP Colorectal Risk Calculator - people

Reference	Bilimoria 2013 [30]
	undergoing colon operations Exclusion criteria: none stated
Target condition(s)	VTE (30 days): not defined. Incidence: all surgery – 12,671 (0.9%); colon surgery – n=3508 (4%)
Risk tool(s)	Universal ACS NSQIP Surgical Risk Calculator Web-based tool with 21 preoperative factors • Age group (<65, 65-74, 75-84, ≥85) • Sex • Functional status (Independent, partially dependent, totally dependent) • Emergency case • American Society of Anaesthesiologists (ASA) Class (1 or 2, 3, 4 or 5) • Steroid use for chronic condition • Ascites within 30 days preoperatively • System sepsis within 48 h preoperatively (None, SIRS, sepsis, septic shock) • Ventilator dependent • Disseminated cancer • Diabetes (No, Oral, Insulin) • Hypertension requiring medication • Previous cardiac event • Congestive heart failure in 30 days preoperatively • Dyspnea • Current smoker within 1 year • History of COPD • Dialysis • Acute renal failure • Body mass index (BMI) Class (Underweight, normal, overweight, obese 1, obese 2, obese 3) • CPT-specific linear risk (2,805 values) ACS NSQIP Colorectal Risk Calculator 22 factors • Age group (<65, 65-74, 75-84, ≥85) • Sex • Functional status (Independent, partially dependent, totally dependent)

Reference	Bilimoria 2013 [30]
	• Emergency case • American Society of Anaesthesiologists (ASA) Class (1 or 2, 3, 4 or 5) • Steroid use for chronic condition • Ascites within 30 days preoperatively • System sepsis within 48 h preoperatively (None, SIRS, sepsis, septic shock) • Ventilator dependent • Disseminated cancer • Diabetes (No, Oral, Insulin) • Hypertension requiring medication • Previous cardiac event • Congestive heart failure in 30 days preoperatively • Dyspnea • Current smoker within 1 year • History of COPD • Dialysis • Acute renal failure • BMI Class (Underweight, normal, overweight, obese 1, obese 2, obese 3) • Colon surgery group (colectomy) (Partial lap with anastomosis, partial lap with ostomy, partial open with anastomosis, partial open with ostomy, total lap with ostomy, total open with ostomy) • Indication for colon surgery (Diverticulitis, enteritis/colitis, haemorrhage, neoplasm, obstruction/perforation, vascular insufficiency, volvulus, other)
Statistical measures	All surgery population: Universal ACS NSQIP Surgical Risk Calculator • C-statistic 0.819 • Brier score 0.009
	Colon surgery population: Universal ACS NSQIP Surgical Risk Calculator • C-statistic 0.7203 • Brier score 0.0218
Source of funding	Part funded by the Agency for Healthcare Research and Quality
Limitations	Predictors: Unclear if predictor assessments were made without knowledge of outcome data

Reference	Bilimoria 2013 [30]
	Outcome: No VTE definition reported, too few events compared to number of factors in the risk tool. Analysis: No relevant performance measures evaluated
Comments	

Reference	Grant 2016 [127]
Study type	Retrospective cohort (data registry)
Study methodology	Recruitment: January 2011 to March 2014, data spanning 63,548 eligible patients across 48 hospitals was collected. Follow-up data are collected through both medical record review and direct telephone follow up at 90 days post-hospital discharge. Validation: External validation
Number of patients	n= 63,548
Patient characteristics	Age: mean 65.8 years (≥ 75 years 35.66%) Gender (male to female ratio): 1:1.4 Ethnicity: not reported Average length of hospital stay: 4.5 days. Prophylaxis: 60.9% received pharmacologic venous thromboembolism prophylaxis Setting: Michigan Hospital Medicine Safety Consortium (48 Michigan hospitals) Country: USA Inclusion criteria: Hospitalised medical patients admitted to a medicine service for two or more days Exclusion criteria: 1) Under the age of 18; 2) pregnant; 3) underwent any surgical procedure during the admission; 4) direct admission to an intensive care unit; 5) direct admission for end-of-life care; 6) diagnosis of venous thromboembolism in the 6 months prior to admission; 7) admitted for presumed venous thromboembolism; 8) admitted under observation status; 9) re-admitted within 90 days of discharge from an admission including in the registry; or 10) received systemic anticoagulation on day one or day two of the index hospitalisation.
Target condition(s)	Clinically-suspected and image-confirmed hospital associated VTE (90 days): Including proximal upper or proximal lower extremity DVT and PE. VTE events must have occurred on the third day after admission or later (up to 90 days after admission). Diagnosis of DVT was based on positive findings via compression Doppler ultrasound or venography, PE was confirmed via computed tomography (CT) scan, ventilation perfusion (V/Q)

Reference	Grant 2016 [127]
	scan or pulmonary angiography Incidence: n= 670 (1.05%)
Risk tool(s)	Caprini Risk Assessment Model (RAM) • Five points allocated to: Stroke, acute spinal cord injury or paralysis (<1 month), Hip, pelvis, or leg fracture (<1 month), multiple trauma (<1 month) • Three points allocated to: age 75 (years), history of VTE, Family history of VTE, History of thrombophilia, HIT • Two points allocated to: age 61-74 (years), positive history of cancer, immobilising plaster cast, patient confide to a bed (≥72 hours) • One point allocated to: age 41-60 (years), congestive heart failure, COPD or abnormal pulmonary function, IBD, severe lung disease, acute MI, Sepsis (<1 month), surgery (<1 month), postpartum (<1 month), history of unexpected stillborn infant, recurrent spontaneous abortion (≥3 month) or premature birth, varicose veins, obesity (BMI > 25), current swollen leg, CVC on admission, immobile/not ambulating, HRT or oral contraceptives.
Statistical measures	Caprini score • Caprini score 5 cut-off: sensitivity 69.70%, specificity 50.28%; PLR 1.4019, NLR 0.6026; PPV 0.01472, NPV 0.99362 • Caprini score 7 cut-off: sensitivity 42.69%, specificity 74.71%; PLR 1.6879, NLR 0.7671; PPV 0.01767, NPV 0.99189 • Caprini score 9 cut-off: sensitivity 18.51%, specificity 89.03%; PLR 1.6875, NLR 0.9153; PPV 0.01766, NPV 0.99034
Source of funding	Blue Cross/Blue Shield of Michigan and Blue Care Network
Limitations	Very serious risk of bias: Retrospective nature of the design means unclear if those assessing predictors retrospectively were aware of outcome data, low event rate compared to number of predictors in the model, no calibration data reported and unclear reference standard used to calculate sensitivity and specificity so 2x2 table unable to be calculated. Applicability issues with US population and risk factor definitions.
Comments	

Reference	Greene 2016[129]
Study type	Prospective cohort

Reference	Greene 2016[129]
Study methodology	Recruitment: Michigan Hospital Medicine Safety (HMS) Consortium. The HMS Consortium is a group of hospitals working to prevent adverse events in hospitalized medical patients in Michigan through creation of a data registry and sharing of best practices. Although participation is voluntary, each hospital receives payments for participating in the consortium and for data collection. Clinical data on patients are collected through a standardized process at each hospital using dedicated, trained medical record abstractors. Patients discharged from each participating hospital were sampled on an 8 day rolling cycle; data on the first 18 eligible cases discharged during the cycle were collected. Validation: External validation [14 ,178 ,303 ,342]
Number of patients	n= 63,548
Patient characteristics	Age: mean 65.8 years (≥ 75 years 35.66%) Gender (male to female ratio): 1:1.4 Ethnicity: not reported Cancer within last year – 7.85% Central venous catheter present on admission – 7.89% Prior VTE – 6.40% Family history of VTE – 0.69% Postpartum (<1 month) – 0.06% Surgery (<1 month) – 2.67% Pneumonia (<1 month) – 14.22% Other acute infection – 13.81% Congestive heart failure – 9.33% Sepsis (<1 month) – 10.32% Obesity (BMI > 30) – 35.20% Myocardial infection (<1 month) – 1.67% Inflammatory bowel disease – 3.17% Stroke – 4.78% Transferred to ICU 1.86% Prophylaxis: 60.9% received pharmacologic venous thromboembolism prophylaxis Setting: 48 Michigan hospitals

Reference	Greene 2016[129]
	Country: USA Inclusion criteria: Those admitted to a medicine service for two days or longer Exclusion criteria: 1) Under the age of 18; 2) pregnant; 3) underwent any surgical procedure during the admission; 4) direct admission to an intensive care unit; 5) direct admission for end-of-life care; 6) diagnosis of venous thromboembolism in the 6 months prior to admission; 7) admitted for presumed venous thromboembolism; 8) admitted under observation status; 9) re-admitted within 90 days of discharge from an admission including in the registry; or 10) received systemic anticoagulation on day one or day two of the index hospitalisation.
Target condition(s)	Hospital associated VTE (90 days): Proximal upper or proximal lower extremity DVT and PE. VTE events must have occurred on the third day after admission or later (up to 90 days after admission). Diagnosis of DVT was based on positive findings via compression Doppler ultrasound or venography, PE was confirmed via computed tomography (CT) scan, ventilation perfusion (V/Q) scan or pulmonary angiography Incidence: n= 670 (1.05%)
Risk tool(s)	<u>Kucher Score</u> • Three points allocated to: cancer, prior VTE, hypercoagulability • Two points allocated to: major surgery • One point allocated to: bed rest, age > 70 years, obesity (BMI > 30), hormone replacement therapy/oral contraceptives <u>Padua Prediction Score</u> Data was also applied to the Padua Prediction Score • Three points were allocated to: active cancer, previous VTE, reduced mobility, already known thrombophilic condition • Two points were allocated to: recent trauma and/or surgery • One point allocated to: elderly age ≥70 years, heart and/or respiratory failure, acute myocardial infarction or ischaemic stroke, acute infection and/or rheumatologic disorder, obesity (BMI ≥30 kg/m2, and on-going hormonal treatment. Patients were classified as high (Padua Prediction Score ≥4) or low (Padua Prediction Score <4) risk of VTE. <u>International Medical Prevention on Venous Thromboembolism (IMPROVE)</u> The following risk factors are given 1-3 points each and pointes are added to achieve a final score which is then categorised into tiers of low (0-1 points), moderate(2-3 points) or high risk of VTE (≥4 points): • Three points allocated to: previous VTE • Two points allocated to: Known thrombophilia, lower limb paralysis, current cancer • One point allocated to: Immobilisation ≥ 7 days, ICU/ CCU stay, age > 60 years <u>Intermountain risk assessment model</u>

Reference	Greene 2016[129]
	Risk factors included in the RAM are: • Prior VTE • An order for bed rest • PICC insertion • Diagnosis of cancer The number of points allocated to each risk factor was not reported. At risk ≥1.
Statistical measures	Kucher Score (at risk ≥4: 10.34%) • C-statistic – 0.563 (0.558-0.568) Padua Prediction Score (at risk ≥4: 16.66%) • C-statistic – 0.600 (0.594-0.606) IMPROVE (at risk ≥2: 11.71%) • C-statistic – 0.570 (0.565-0.576) Intermountain risk assessment model (at risk ≥1: 19.13%) • C-statistic – 0.611 (0.605-0.618)
Source of funding	Blue Cross/Blue Shield of Michigan and Blue Care Network
Limitations	Risk of bias introduced by analysis: relevant performance measures were not evaluated (sensitivity and specificity) for all four risk tools Applicability issues with US population and risk factor definitions.
Comments	

Reference	Hachey 2016 [132]
Study type	Retrospective cohort
Study methodology	Recruitment: people who underwent segmenectomy, lobectomy or pneumonectomy for lung cancers within the Division of Thoracic Surgery were identified between June 2005 and June 2013. Pertinent cases were selected based on current procedural terminology for open and minimally invasive operations, and all cases were included that matched the ICD-9 codes for non-small cell lung cancers and small cell lung cancers. Validation: External validation in multiple specialties including general, vascular, plastic surgery and gynaecologic oncology [251];[12];[43];[307];[345].

Reference	Hachey 2016 [132]
Number of patients	n=232
Patient characteristics	Age: Adults (with VTE mean 63.83±10.2 years, without VTE mean 64.36±11 years) Gender (male to female ratio): 100:132 Ethnicity: not reported Condition(s): lung cancer Surgery: lobectomy (84.5%), segmenectomy (8.2%), pneumonectomy (7.3%) Prophylaxis: pharmacological with VTE 100%, without VTE 91.8%; intermittent pneumatic compression with VTE 100%, without VTE 91.8% BMI (kg/m^2): with VTE mean 27.38±5.05, without VTE mean 27.42±7.02 Setting: 1 hospital Country: USA Inclusion criteria: documentation of at least 60 day follow up; received routine postoperative, prophylactic, subcutaneous, unfractionated heparin 3 times daily, and/or intermittent pneumatic compression during the hospitalisation Exclusion criteria: lost to follow-up or missing records; deceased due to non-VTE causes before 60 days after surgery; multiple operations after the first; preoperative inferior vena cava filter placement; and hospital discharge on therapeutic anticoagulation for indications not related to postoperative VTE
Target condition(s)	VTE (60 days): defined as any PE or DVT identified via clinical imaging studies (i.e., computed tomography pulmonary angiogram or duplex ultrasound) and treated with therapeutic anticoagulation or inferior vena cava filter. Incidence n=12 (5.2%)
Risk tool(s)	Caprini score Total score is used to place people in one of three main risk categories: low (scores 0-4), moderate (5-8) and high (≥9). Score 1: • Age 40-59 (years) • Abnormal pulmonary function • Acute myocardial infarction (<1 month) • BMI ≥30 (kg/m2) • Congestive heart failure (<1 month) • History of inflammatory bowel disease

Reference	Hachey 2016 [132]
	• History of prior major surgery (<1 month) • Complications of pregnancy (history of unexplained stillborn infant, recurrent or spontaneous abortion (>3), premature birth with toxemia of pregnancy, or growth-restricted infant) • Oral contraceptive use or HRT • Sepsis (<1 month) • Serious acute lung disease (<1 month) • Swollen legs (current) • Varicose veins Score 2: • Age 60-74 (years) • Central venous access • Confined to bed (>72 hours) • Major open surgery (≥45 minutes) • Present cancer • Prior cancer, except nonmelanoma skin Score 3: • Age ≥75 (years) • History of VTE • Family history of VTE • Chemotherapy • Positive anticardiolipin antibody • Positive Lupus anticoagulant • Acute spinal cord injury (<1 month) • Major surgery (≥6 hours)
Statistical measures	Caprini score • Score >5: Sensitivity 100 (100 – 100); Specificity 7.2 (4.1 – 11) • Score >7: Sensitivity 100 (100 – 100); Specificity 31.4 (25 – 37.3) • Score >9: Sensitivity 83.3 (58.3 – 100); Specificity 60.5 (54.4 – 67.3) • Score > 10: Sensitivity 75 (50 -100); Specificity 69.6 (64.4 – 76.4) • C-statistic 0.72 • PPV 10.3 • NPV 98.5

Reference	Hachey 2016 [132]
	• Hosmer-Lemeshow test p=0.61
Source of funding	Not reported
Limitations	Predictors: Unclear if predictor assessments were made without knowledge of outcome data Sample size and participant flow: There was not a reasonable number of outcome events compared to number of factors in the model
Comments	

Reference	Hegsted 2013 [142]
Study type	Retrospective cohort
Study methodology	Data source: The cohort was identified from the prospectively defined trauma registry for the years 2003 and 2006. Data elements were obtained from the trauma registry, chart abstraction, and manual calculation of RAP Validation: Externally validated within a cohort analysis involving 184 trauma patients in 2000 [118]
Number of patients	n=2281
Patient characteristics	Age (mean): 45.2 years Gender (male to female ratio): 2.33:1 Ethnicity: not reported Condition(s): People with trauma (not details provided about type of trauma) Setting: Level I trauma centre Country: USA Inclusion criteria: Patients aged 13 years and older admitted to a level I trauma center and hospitalised for longer than 48 hours. Exclusion criteria: None reported
Target condition(s)	DVT (definition not reported) (time point unclear) PE detected by computed tomography-angiography or post-mortem examination (time point unclear) Prevalence: DVT n= 239 (10.5%), PE n=34 (1.5%)

Reference	Hegsted 2013 [142]
Risk tool(s)	Risk Assessment Profile (RAP) Each patient's risk for the development of VTE is defined by RAP score and categorised as being at low (RAP ≤5), medium/moderate (RAP≤14) or high (RAP>14) risk. Risk factors: • Four points allocated to: complex lower extremity fracture, pelvic fracture, spinal cord injury, paraplegia or quadriplegia, ≥75 years old • Three points allocated to: history of thromboembolism, repair or ligation of major vascular injury, spinal fractures, GCS <8 for >4 hours, 60 ≥ but <75 years • Two points allocated to: obesity, malignancy, abnormal coagulation, central femoral line >24 hours, transfusion more than 4 units in 24 hours, surgery >2 hours, chest AIS >2, abdomen AIS >2, head AIS >2, ≥40 but <60 years
Statistical measures	RAP Outcome: DVT • Moderate cut-off (5 to ≤ 14): Sensitivity 82% (77-87%); Specificity 57% (55-59%) ; PPV 18% (16-21%); NPV 96% (95-97%) • High cut-off (>14): Sensitivity 15% (11-20%); Specificity 97% (97-98%); PPV 41% (31-51%); NPV 91% (90-92%) Outcome: PE • Moderate cut-off (5 to ≤ 14): Sensitivity 71% (55-86%); Specificity 53% (51-56%) ; PPV 2% (1-3%); NPV 99% (99-100%) • High cut-off (>14): Sensitivity 12% (1-23%); Specificity 96% (95-97%) ; PPV 4% (0-9%) ; NPV 99% (98-99%)
Source of funding	This study was supported by Legacy Health Research Foundation
Limitations	Patient selection: Unclear if patients were enrolled at a similar state of health and if inclusions and exclusions were appropriate. Predictors: Unclear if predictor assessments were made without knowledge of outcome data Outcome: time point unclear for target conditions and definition for one of the target conditions not reported
Comments	

Reference	Hewes 2015 [146]
Study type	Retrospective cohort

Reference	Hewes 2015 [146]
Study methodology	Data source: records of patients who underwent an oesophagectomy for cancer by the thoracic surgery service between June 2005 and June 2013 were reviewed. The Caprini risk score and the number of VTE events were recorded retrospectively for each patient. Patients were identified by the oesophagectomy Current Procedural Terminology cods I the thoracic surgery billing lists and then cross-correlated with the ICD codes for cancer. Validation: Externally validated in multiple surgical specialities [126,251,12,43,307,345]
Number of patients	n=70
Patient characteristics	Age: with VTE mean 64.9±6.4, without VTE mean 61.6±11.7 Gender (male to female ratio): 58:12 Ethnicity: white 70%, black 20%, Asian or Pacific Islander 2.9%, Hispanic 2.9% Condition(s): oesophageal cancer Surgery: oesophagectomy BMI (kg/m^2 (IQR)): with VTE 26.9 (9.7), without VTE 25.1 (6.9) Setting: 1 hospital Country: USA Inclusion criteria: diagnosis of oesophageal cancer treated with oesophagectomy (any approach) and with available 60-day postoperative follow-up Exclusion criteria: patients with missing records and with incomplete follow-up; the presence of an inferior vena cava filter or chronic anticoagulation therapy
Target condition(s)	VTE (60 days): defined as any thromboembolic event diagnosed by appropriate imaging findings and treated with therapeutic anticoagulation or inferior vena cava filter. Incidence: n= 10 (14.3%)
Risk tool(s)	<u>Modified Caprini risk assessment model (1 – 60 days)</u> Assigned score was the sum of the risk factors accrued before the first occurrence of one of the following: date of maximum Caprini score, date of discharge, or within 24 hours before VTE diagnosis. Standardised case definitions for each risk factor were established for homogeneity of review among the chart reviewers. For sepsis, systemic inflammatory response syndrome criteria were used. Score 1: • Age 41-59 (years)

Reference	Hewes 2015 [146]
	• Abnormal pulmonary function • Acute myocardial infarction (<1 month) • BMI ≥30 (kg/m2) • Congestive heart failure (<1 month) • History of inflammatory bowel disease • History of prior major surgery (<1 month) • Sepsis (<1 month) • Serious acute lung disease (<1 month) • Swollen legs (current) • Varicose veins • Minor surgery planned • Medical patient currently on bed rest • Leg plaster cast or brace • Central venous access Score 2: • Age 60-74 (years) • Major surgery (> 60 minutes) • Previous malignancy • Arthroscopic surgery (>60 minutes) • Laparoscopic surgery (>60 minutes) • Morbid obesity (BMI> 40 kg/m2) Score 3: • Age ≥75 (years) • History of SVT, DVT/PE • Family history of VTE • Present cancer or chemotherapy • Positive anticardiolipin antibody • Positive Lupus anticoagulant

Reference	Hewes 2015 [146]
	• Acute spinal cord injury (<1 month) • Major surgery (2-3 hours) • BMI > 50 kg/m2 (venous stasis syndrome) • Congenital thrombophilia: positive factor V Leiden, positive prothrombin 20210A, elevated serum homocysteine • Acquired thrombophilia: positive lupus anticoagulant, elevated anticardiolipin antibodies, HIT • Other thrombophilia Score 5: • Elective major lower extremity athroplasty • Hip, pelvis or leg fracture (<1 month) • Stroke (<1 month) • Multiple trauma (<1 month) • Acute spinal cord injury (paralysis) (<1 month) • Major surgery >3 hours Further details provided in other studies. [126,251,12,43,307,345]
Statistical measures	<u>Modified Caprini RAM</u> • Cut-off score >15: Sensitivity 100 (100 – 100); Specificity 66.7 (55 – 78.3) • PPV 33.3% • NPV 100% (FP n=20, FN n=0) • C-statistic 0.818 (0.7111 – 0.908) • Hosmer-Lemeshow goodness of fit test 10.282 (6) *p*=0.113
Source of funding	National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program grant
Limitations	Predictors: Unclear if predictor assessments were made without knowledge of outcome data Sample size and participants: There was not a reasonable number of outcome events and unclear if all enrolled participants were included in the analysis
Comments	

Reference	Ho 2014 [148]
Study type	Retrospective cohort
Study methodology	Data source: This study utilised the VTE data from two datasets of major trauma patients who were admitted to the Royal Perth Hospital in Western Australia. The first dataset contained 134 consecutive patients who died after major trauma between 1994 and 2002 with accurate information on the causes of death including those who had fatal PE. The second dataset contained 224 consecutive patients who required an IVC filter between 2007 and 2012 for either primary or secondary VTE prophylaxis due to contraindications to pharmacological VTE prophylaxis or treatment. Both datasets contained the five variables needed by the TESS to calculate the predicted risk of VTE. The clinical information recorded within the first 24 hours of trauma admission prior to the occurrence of VTE was used to generate the predicted risk of VTE by the TESS for each patient in this study. Validation: External validation in trauma population [278]
Number of patients	n=357
Patient characteristics	Age: mean (IQR): VTE event 42 (23-55) years; No VTE event 31 (21-45) years Gender (male to female ratio): VTE event 3.6:1; No VTE event 2.82:1 Ethnicity: Not reported Condition(s): Trauma patients Chest injury: 61.9% Abdominal injury: 29.1% Spinal fractures: 43.4% Pelvic fractures: 32.8% Lower limb fractures: 38.4% Setting: Royal Perth Hospital, a university teaching hospital, Western Australia's largest trauma centre. Country: Australia Inclusion criteria: Major trauma patients Exclusion criteria: not reported
Target condition(s)	VTE (time point unclear): DVT and PE confirmed by colour Doppler compression ultrasound and computed tomography pulmonary angiography or post mortem examination.

Reference	Ho 2014 [148]
	Prevalence: Overall VTE: n=74 (21%); Fatal PE: n= 16 (4.48%); Non-fatal PE: 22 (6.16%; DVT: 47 (13.17%). 3 people had concurrent PE and upper and lower limb DVT, 3 patients had concurrent upper and lower limb DVT and 2 patients had concurrent lower limb DVT and PE.
Risk tool(s)	Trauma Embolic Scoring System (TESS) The scoring system requires data from five clinical variables for a score (score per variable not reported in study) • Injury Severity Score • Age • Use of mechanical ventilation • Obesity status • Lower limb injuries
Statistical measures	TESS (<9) Outcome: VTE • Sensitivity: 97% (91-99%) • Specificity: 27% (22-32%) • PPV: 26% (21-31%) • NPV: 97% (91-99%) • C-statistic: 0.71 (0.65-0.77) Fatal and non-fatal PE • Sensitivity: 97% (87-99%) • Specificity: 24% (20-29%) • PPV: 13% (10-18%) • NPV: 99% (93-99%) • C-statistic: 0.67 (0.59-0.75) Fatal PE • Sensitivity: 100% (81-100%) • Specificity: 20% (13-28%) • PPV: 14% (9-22%) • NPV: 100% (86-100%) • Hosmer-Lemeshow test – p=13.7

Reference	Ho 2014 [148]
Source of funding	Department of Intensive Care Medicine, Royal Perth Hospital
Limitations	Patient selection: Unclear study inclusion and exclusion criteria Predictors: Unclear if predictor assessments were made without knowledge of outcome data Analysis: No relevant performance measures evaluated Outcome: unclear time point for target conditions
Comments	

Reference	Liu 2014 [209]
Study type	Prospective cohort
Study methodology	Data source: The following variables were prospectively recorded on separate case report forms: age, gender, BMI, smoking habit, hypertension, diabetes, atrial fibrillation. TIA, ischemic heart disease, malignancy, history of VTE, and treatment methods (medical treatment, and the use of elastic stockings). The presence of clinical symptoms or signs of DVT/PE at any stage during the study period was noted. Ischemic stroke phenotypes were determined by the Oxfordshire Community Stroke Project classification. At each Doppler scan, the NIHSS score was assessed by a certified trial coordinator. Validation: Internal split half validation
Number of patients	n=287
Patient characteristics	Age: ≥65 years 58.2% Gender (male to female ratio): 1.68:1 Ethnicity: Not reported. Condition(s): Acute stroke patients Obesity (BMI ≥ 25 kg/m2): 40.8% Active cancer: 2.4% Vein puncture: 3.8% Setting: Capital Medical University affiliated Tiantan Hospital Country: China

Reference	Liu 2014 [209]
	Inclusion criteria: older than 18; had acute stroke (ischemic or haemorrhagic) within 7 days; mRS ≥ 2 before enrolment; weakness in the lower limbs with NIH Stroke Scale score of ≥1 on item VI; able to obtain consent from the patient, patient's legal representative. Exclusion criteria: TIAs, subarachnoid haemorrhage (SAH), brain tumour, cerebral venous thrombosis, history of VTE.
Target condition(s)	DVT (14±3 days): Diagnosis of DVT if complete compression duplex ultrasonography (CCUS) showed loss of vein compressibility by ultrasonic probe pressure, a clot, or an abnormal flow pattern (loss of phasic flow signal or loss of augmentation of flow) with distal compression Prevalence: n=30 (10.6%)
Risk tool(s)	Poststroke DVT Prediction System A multivariable model that predicts DVT risk at 14 days for patients admitted with an acute stroke, developed using data from the assessment cohort. The final multivariate model predicting DVT after acute stroke contained six variables which increased the risk of DVT: One point allocated to: • Older age (≥65 years) • Female gender • Obesity (BMI ≥ 25 kg/m2) • Haemorrhagic stroke subtype • Lower limb NIHSS score ≥2 Two points allocated to: • Active cancer The probability of post-stroke DVT incidence was estimated by summing points assigned to the value of each predictor. Total point score ranges from 0 to 7.
Statistical measures	Post-stroke DVT Prediction System • C-statistic: 0.65 (0.59-0.70)
Source of funding	The study was supported by Beijing Natural Science Foundation, the Ministry of Science and Technology and the Ministry of Health of the People's Republic of China. The study was also supported by the GlaxoSmithKline (China) Ltd.
Limitations	Analysis: Missing some relevant performance measures evaluated Sample size and participant flow: There was not a reasonable number of outcome events compared to the number of predictors in the model
Comments	

Reference	Lobastov 2016 [210]
Study type	Prospective cohort retrospectively analysed
Study methodology	Data source: Data collected prospectively through a form designed for the study to be filled out by investigators during observation period according to medical records, examination of the patient and results od duplex scanning. Patients assessed using the Caprini model on completion of the study (achieving an end point, being discharged from hospital or lethal outcome). Validation: External validation
Number of patients	n=140
Patient characteristics	Age, mean (SD; range): 69.2 (12.2; 40-83) Gender (male to female ratio): 68:72 Ethnicity: Not reported. All surgical interventions were made in an emergency manner General surgical n=67 Neurosurgical n=73 Primary pathological condition: Cerebral and meningeal tumours n=7 Parenchymal intracranial haemorrhage n=24 Non-traumatic subarachnoid, subarachnoid-parenchymal haemorrhage n=23 Traumatic intracranial haemorrhage n=19 Intestinal gangrene n=12 Purulent peritonitis n=13 Malignant gastrointestinal tumours n=38 Thoracic and abdominal penetrating wounds n=4 All patients received the standard post-operative VTE prophylaxis for high-risk people: 18 to 21 mmHg compression hospital stockings and UFH 5000IU dose three times a day. Setting: Multi clinical sites including Pirogov Russian National Research Medical University, Moscow Clinical Hospital No 12, and no 13, Clinical

Reference	Lobastov 2016 [210]
	Hospital no 1 of the President's Administration of the Russian Federation. Country: Russia Inclusion criteria: Age older than 40 years, history of major surgery, a high risk of post-operative VTE and informed consent. Initial VTE classification based on 2008 ACCP guidelines (classifies high risk as ages 40-60 and presence of risk factors similar to Caprini model. Exclusion criteria: History of partial occlusion of inferior vena cave, no anticoagulant prophylaxis effect 5 days after surgery, need for therapeutic anticoagulants, preoperative use of anticoagulants, coagulopathies, thrombocytopenia, haemorrhagic diathesis, lower limb soft tissue infections, ankle-brachial index <0.6 or >1.3, patient death within the first 5 days of surgery, or refusal of autopsy.
Target condition(s)	Fresh DVT or PE at the hospital treatment stage – occlusion of previously unaffected vein segments: duplex ultrasonography of the lower limbs, and static lung perfusion scintigraphy or combined single proton emission CT and x-ray CT of the lungs, or autopsy. Incidence: 39/140 (27.83%)
Risk tool(s)	Caprini score Total score is used to place people in one of three main risk categories: low (scores 0-4), moderate (5-8) and high (≥9). Score 1: • Age 41-60 (years) • Swollen legs (current) • Varicose veins • BMI >25 (kg/m2) • Minor surgery planned • Sepsis (<1 month) • Acute myocardial infarction (<1 month) • Congestive heart failure (<1 month) • Medical patient currently receiving bed rest • History of inflammatory bowel disease • History of prior major surgery (<1 month) • Abnormal pulmonary function • Serious acute lung disease (<1 month) • Oral contraceptive use or hormone replacement therapy (HRT) • Complications of pregnancy (history of unexplained stillborn infant, recurrent or spontaneous abortion (>3), premature birth with toxaemia of pregnancy, or growth-restricted infant)

Reference	Lobastov 2016 [210]
	Score 2: • Age 61-74 (years) • Arthroscopic surgery • Malignancy (present or previous) • Laparoscopic surgery (>45 minutes) • Confined to bed (>72 hours) • Immobilising plaster cast • Central venous access • Major surgery (≥45 minutes) Score 3: • Age ≥75 (years) • History of VTE • Positive Factor V Leiden • Increased serum homocysteine level • HIT • Positive anticardiolipin antibody • Positive prothrombin 20210A • Positive Lupus anticoagulant • Other congenital or acquired thrombophilia Score 5: • Stroke (<1 month) • Multiple trauma (<1 month) • Elective major lower extremity arthroplasty • Hip, pelvis or leg fracture (<1 month) • Acute spinal cord injury (paralysis) (<1 month)
Statistical measures	Caprini risk assessment model • At 10.5% cut off – sensitivity 0.95, specificity 0.73 • C-statistic: 0.87 (0.81-0.93)
Source of funding	None stated
Limitations	Analysis: Prospective collection of risk factors but retrospective calculation of full risk tool score means unclear whether predictor assessments

Reference	Lobastov 2016 [210]
	made without knowledge of outcome and vice versa. Sample size and participant flow: There was not a reasonable number of outcome events compared to the number of predictors in the model. Applicability: Patients already assessed as high risk for VTE and receiving combination pharmaceutical and mechanical prophylaxis. Only really applicable if assessing those who are very high risk and may need increased prophylaxis from that offered as usual.
Comments	

Reference	Nendaz 2014 [237]
Study type	Prospective cohort
Study methodology	Data source: Data was collected by physician-investigators or dedicated study coordinators and entered in a standardised electronic case report form between December 2010 and November 2011. Validation: Externally validated [14]
Number of patients	n=1478
Patient characteristics	Age: 65%(>60 years); 44% (≥ 70 years) Gender (male to female ratio): not reported Ethnicity: not reported Condition(s): Acutely medically ill patients Immobilisation: 37.2% Acute infection/sepsis: 30% Active malignancy: 25.4% Respiratory failure: 23.9% Obesity (BMI >30): 14.8% Cardiac failure: 12% Dehydration: 11.3% Prior VTE: 8.2% Chronic venous insufficiency: 6.6%

Reference	Nendaz 2014 [237]
	Recent trauma or surgery ≤ 1month: 6.4% Hormonal therapy: 4.7% Acute inflammatory/rheumatic disease: 4.1% Recent travel for >6 hours: 3.4% Recent myocardial infarction: 2.2% Myeloprofilerative syndrome: 2.1% Recent stroke <3 months: 2.1% Nephrotic syndrome: 1.6% Known thrombophilia: 0.6% Pregnancy: 0.2% Setting: Three academic and five non-academic acute care hospitals Country: Switzerland Inclusion criteria: Aged ≥18 years and admission to a medical ward with a minimum stay of >24 hours Exclusion criteria: Anticoagulant treatment or indication of therapeutic anticoagulation upon hospital admission and inability to provide informed consent
Target condition(s)	Symptomatic VTE (90 days) including PE or DVT. PE was confirmed by contrast-enhanced computer tomography, ventilation perfusion scan or conventional pulmonary angiography, and DVT by compression ultrasound or venography. Prevalence: n= 30 (2.3%)
Risk tool(s)	<u>Geneva Risk Score</u> Was calculated after patient discharge, from data at hospital admission. • Two points allocated to: cardiac failure, respiratory failure, recent stroke (<3 months), recent myocardial infarction (<4 weeks), acute infectious disease (including sepsis), acute rheumatic disease, active cancer, myeloproliferative syndrome, nephrotic syndrome, prior VTE, and known hypercoagulable state. • One point allocated to: immobilisation (complete bed rest or inability to walk for >30 minutes per day), recent travel >6 hours, age >60 years, body mass index [BMI] > 30 kg/m2, chronic venous insufficiency, pregnancy, hormonal therapy, and dehydration (assessed subjectively by the treating physician). Patients were classified as having a high (Geneva Risk Score ≥3) or low (Geneva Risk Score <3) risk of VTE.

Reference	Nendaz 2014 [237]
	Padua Prediction Score Data was also applied to the Padua Prediction Score • Three points were allocated to: active cancer, previous VTE, reduced mobility, already known thrombophilic condition • Two points were allocated to: recent trauma and/or surgery • One point allocated to: elderly age ≥70 years, heart and/or respiratory failure, acute myocardial infarction or ischaemic stroke, acute infection and/or rheumatologic disorder, obesity (BMI ≥30 kg/m2, and on-going hormonal treatment. Patients were classified as high (Padua Prediction Score ≥4) or low (Padua Prediction Score <4) risk of VTE.
Statistical measures	Geneva Risk Score (<3) Sensitivity: 90% (73.5-97.9%) Specificity: 35.3% (32.8-37.8%) PPV: 2.8% (1.9-4.1%) NPV: 99.4% (98.3-99.9%) NLR: 0.28 (0.10-0.83) Padua Prediction Score (≥4) Sensitivity: 73.3% (54.1-87.7%) Specificity: 51.9% (49.3-54.5%) PPV: 3.1% (2.0-4.7%) NPV: 98.9% (97.9-99.5%) NLR: 0.51 (0.28-0.94)
Source of funding	This study was funded by an unrestricted educational grant from the International Society of Thrombosis and Haemostasis (ISTH), 2007 Presidential Fund and Sanofi-Aventis (Suisse) SA, Vernier, Switzerland
Limitations	Sample size and participant flow: There was not a reasonable number of outcome events
Comments	

Reference	Obi 2015[243]
Study type	Retrospective cohort

Reference	Obi 2015[243]
Study methodology	Data source: data from admissions to a 20-bed SICU, 5 year period (July 1, 2007-June 30, 2012). Patients were retrospectively identified with internal billing and quality improvement records. Validation: External validation[12]
Number of patients	n=4844
Patient characteristics	Age: <41 years 15.9%; 41-60 years 40%; 61-74 years 29.4%; ≥75 years 14.8% Gender (male to female ratio): not reported Ethnicity: not reported Condition(s): Surgical patients including general surgery, transplant, urology, and orthopaedic patients and patients with respiratory failure requiring extracorporeal membrane oxygenation (82% major operative procedures) Setting: SICU, a large tertiary care academic hospital Country: USA Inclusion criteria: Critically ill postsurgical patients and patients with respiratory failure with a mean Acute Physiology and Chronic Health Evaluation score greater than 50 Exclusion criteria: Patients younger than 18 years
Target condition(s)	VTE (time point unclear): defined as patients with DVT or PE which occurred during the patient's initial hospital admission. Investigation for VTE was at the discretion of the ICU and/or surgical attending physicians because no formal screening was in place. DVT included acute thrombosis of lower-extremity veins (iliac, femoral, popliteal, or calf veins) or upper-extremity veins (axillary, subclavian, brachial, or internal jugular veins). PE defined as acute thrombosis within the pulmonary vasculature. VTE considered present if identified with an objective imaging study, including duplex ultrasonography or PE protocol computed tomography. Patients who experienced sudden death were included if post-mortem examination documented definitive evidence of VTE Prevalence of DVT: n=308 (6.4%) Prevalence of PE: n=79 (1.6%)
Risk tool(s)	Caprini score Total score is used to place people in one of three main risk categories: low (scores 0-4), moderate (5-8) and high (≥9). Score 1:

Reference	Obi 2015[243]
	• Age 40-59 (years) • Abnormal pulmonary function • Acute myocardial infarction (<1 month) • BMI ≥30 (kg/m2) • Congestive heart failure (<1 month) • History of inflammatory bowel disease • History of prior major surgery (<1 month) • Complications of pregnancy (history of unexplained stillborn infant, recurrent or spontaneous abortion (>3), premature birth with toxemia of pregnancy, or growth-restricted infant) • Oral contraceptive use or hormone replacement therapy (HRT) • Sepsis (<1 month) • Serious acute lung disease (<1 month) • Swollen legs (current) • Varicose veins Score 2: • Age 60-74 (years) • Central venous access • Confined to bed (>72 hours) • Major open surgery (≥45 minutes) • Present cancer • Prior cancer, except non-melanoma skin Score 3: • Age ≥75 (years) • History of VTE • Family history of VTE • Chemotherapy • Positive anticardiolipin antibody • Positive Lupus anticoagulant • Acute spinal cord injury (<1 month) • Major surgery (≥6 hours)
Statistical measures	Caprini risk assessment model

Reference	Obi 2015[243]
	C-statistic: 0.5846 Hosmer and Lemeshow test: p=0.69
Source of funding	Not reported
Limitations	Analysis: No relevant performance measures evaluated Outcome: unclear time point for measurement of target condition (VTE)
Comments	

Reference	Pannucci 2012 [253]
Study type	Retrospective cohort
Study methodology	Data source: Data from the American Burn Association's National Burn Repository was obtained, it is a voluntary dataset composed of burn patients from participating centres in both United States and Canada. Patients with DVT and VTE were identified using the complications database Validation: Internal split half validation
Number of patients	n=5761
Patient characteristics	Age (mean): 45.6 years Gender (male to female ratio): 2.33:1 Ethnicity: Not reported Condition(s): People with thermal injury (details not reported about types of burns) Setting: Not reported Country: USA and Canada Inclusion criteria: Patients from the NBR admitted between 1995 and 2009 with age ≥ 18 years and length of stay at least 2 days Exclusion criteria: Patients with non-thermal injury (desquamating skin disease, radiation associated burns, and electrical injury) and patients who died within 3 days of admission were excluded.
Target condition(s)	VTE (time point unclear: not defined). Prevalence: n=1635 (9.7%)

Reference	Pannucci 2012 [253]
Risk tool(s)	Simple Venous Thromboembolism Risk Scoring Tool Independent variables used in the analysis were TBSA burned, inhalation injury, gender and age. Score = 0-8 Scoring details were not provided for each factor within the risk scoring tool.
Statistical measures	Simple Venous Thromboembolism Risk Scoring Tool • C-statistic – 0.750
Source of funding	Supported by NIH grant
Limitations	Predictors: Unclear if predictor assessments were made without knowledge of outcome data Sample size and participant flow: There was not a reasonable number of outcome events Analysis: No relevant performance measures evaluated Outcome: target condition not defined and unclear time point
Comments	

Reference	Pannucci 2014 [252]
Study type	Retrospective cohort
Study methodology	Data source: Analyses of identified Michigan Surgical Quality Collaborative (MSQC) data. Data acquisition took place between March 2010 and October 2012. Validation: Internal split population validation
Number of patients	n=3576
Patient characteristics	Overall age: ≥ 60 years: 62% Overall gender (male to female ratio): 1:1.36 Ethnicity: not reported Condition(s): Postsurgical patients (details of surgical procedures not provided for validation sample)

Reference	Pannucci 2014 [252]
	Setting: 52 Michigan hospitals, Blue Cross Blue Shield of Michigan, and the Blue Care Network Country: USA Inclusion criteria: Inpatient, non-emergent surgical cases. Exclusion criteria: Age < 18 years and admission for palliative care. Patients with recently diagnosed VTE for which they were actively receiving anticoagulation treatment were also excluded.
Target condition(s)	VTE (90 days): Patients with either PE or PE. Upper extremity DVT included clots in the jugular, subclavian, axillary, or brachial veins. Lower extremity DVT included clots in the vena cava, femoral, tibial, or popliteal veins. Visceral DVT (e.g. portal or mesenteric vein) or cerebral sinus thrombosis were not included in the primary outcome. PE included clots in the pulmonary vasculature. All VTE events were diagnosed using an objective imaging study. Prevalence: n= 50 (1.40%)
Risk tool(s)	Unnamed (Pannucci 2014) Risk model included risk factors: • One point allocated to: Age ≥ 60 years, BMI ≥ 40 kg/m2 • Two points allocated to: Male sex • Three points allocated: Sepsis/septic shock/systemic inflammatory response syndrome (SIRS), personal history of VTE • Four points allocated to: Family history of VTE • Five points allocated: Current cancer
Statistical measures	Unnamed risk assessment model • C-statistic – 0.70
Source of funding	Not reported
Limitations	Sample size and participant flow: There was not a reasonable number of outcome events Analysis: Some relevant performance measures were not evaluated (sensitivity and specificity)
Comments	

Reference	Patell 2017 [256]
Study type	Retrospective cohort

Reference	Patell 2017 [256]
Study methodology	Data source: Consecutive oncology inpatients at the Cleveland Clinic from 11/2012 to 12/2014. Electronic query system of electronic health records. Validation: External validation in cancer outpatients.
Number of patients	n=2780
Patient characteristics	Age, median (range): 62 (19-98) Gender (male to female ratio): 1545:1235 Ethnicity: not reported. Solid tumours 62% Tumour sites: GI tract 20% Lung 13% Breast 6% Head and neck 5% Hematological malignancy 38% Sites: Leukaemia 14%l Lymphoma 14% Myeloma 8% Reasons for admission; Elective chemotherapy 21% Infection 20% GI symptoms 14% Setting: Single centre, Cleveland Clinic Country: USA

Reference	Patell 2017 [256]
	Inclusion criteria: Diagnosis of malignancy and care provided by a haematologist/oncologist admitted to the Cleveland Clinic. Patients over the age of 18 with an active malignancy at the time of admission. Exclusion criteria: VTE on admission, incomplete KS data.
Target condition(s)	VTE: defined by ICD-9 codes. Events coded as not present on index admission. Prevalence: n= 106 (3.8%)
Risk tool(s)	Khorana Score • 0 = low • 1-2 = intermediate • ≥3 high
Statistical measures	Khorana Score • Sensitivity 18.8679 • Specificity 87.1728 Calculated using 2x2 table data based on number reported as high risk on KS (n=363), prevalence of VTE (n=106) and number of those assessed as high risk developing a VTE (n=20) based on Table 1 page 502.
Source of funding	Research support from the National Heart, Lung, and Blood Institute, the Sondra and Stephen Hardis Chair in Oncology Research and the Scott Hamilton CARES Initiative.
Limitations	Predictors: Unclear if predictor assessments were made without knowledge of outcome data Outcome: Unclear if outcome assessed without knowledge of predictor information. Unclear time interval.
Comments	

Reference	Rogers 2012 [278]
Study type	Retrospective cohort
Study methodology	Data source: Analysis for 234,032 consecutive trauma admissions between 2000 and 2009. Derivation: A literature review identified 19 variables associated with VTE for patients with trauma. Of these, 13 variables were found to be significant predictors of VTE by univariate analysis. These variables were integrated into a multivariate logistic model, and five of these risk factors proved significant for the development of VTE and these were integrated into the model. The five risk factors included were: Age, Injury Severity Score (ISS), pre-existing obesity, ventilation days, lower-extremity fracture. Validation: Internal split half validation using the National Trauma Data Bank (NTDB) for the 2007 data using 234,032 patients.

Reference	Rogers 2012 [278]
Number of patients	n=234,032
Patient characteristics	Age: <30 years 40.9%, 30-64 years 41.7%, ≥65 years 17.4%. Median (IQR) 37 (21-56) Gender (male to female ratio): 1.92:1 Ethnicity: not reported. Condition(s): People with trauma Other relevant characteristics: Injury type: blunt 86.9%, burn 2.5%, penetrating 10.6% (missing data for 26,928) Setting: Lancaster General Hospital, a Pennsylvania State Trauma Foundation Level II trauma centre Country: USA Inclusion criteria: People with trauma (no further details reported). Exclusion criteria: Not reported.
Target condition(s)	VTE (no time point reported): DVT and PE as defined by the NTDB data set dictionary definitions. Full definitions not reported in study. PE: Defined as a lodging of a blood clot in a pulmonary artery with subsequent obstruction of blood supply to the lung parenchyma. The blood clots usually originate from the deep leg veins or the pelvic venous system. Consider the condition present if the patient has a V-Q scan interpreted as high probability of pulmonary embolism or a positive pulmonary arteriogram or positive CT angiogram. DVT: The formation, development, or existence of a blood clot or thrombus within the vascular system, which may be coupled with inflammation. This diagnosis may be confirmed by a venogram, ultrasound, or CT. The patient must be treated with anticoagulation therapy and/or placement of a vena cava filter or clipping of the vena cava. Prevalence: n= 4881 (1.4%)
Risk tool(s)	Trauma Embolic Scoring System (TESS) TESS was from 0-14, was used to identify low, moderate, high and very high-risk patients for VTE complications. Individually standardised VTE prophylaxis strategies for each of these four categories were created to address the particular risk. • Injury Severity Score • Age

Reference	Rogers 2012 [278]
	• Use of mechanical ventilation • Obesity status • Lower limb injuries
Statistical measures	TESS • TESS score ≥5: Sensitivity 77.4%; Specificity 75.6%; PPV 4.1%, NPV 99.6% • C-statistic : 0.84 (0.83-0.84) • Hosmer-Lemeshow test – p=0.101
Source of funding	No funding stated
Limitations	Patient selection: Unclear study inclusion and exclusion criteria, unclear if patients enrolled at a similar state of health Predictors: Unclear if predictor assessments were made without knowledge of outcome data
Comments	

Reference	Rothberg 2011 [279]
Study type	Retrospective cohort
Study methodology	Data source: patients discharged between 1 January 2004 and 30 June 2005 from 374 acute care facilities that participated in Premier's Perspective, a database developed for measuring quality and healthcare utilization. Participating hospitals represented all areas of the US. Available data elements include those derived from the uniform billing 04 form, such as socio-demographic information about each patient, their ICD-9-CM diagnosis and procedure codes, as well as hospital and physician information. This information was supplemented with a date-stamped log of all items and services billed to the patient or insurer, including diagnostic tests, medications and other treatments. Derivation: univariate predictors of VTE were assessed using chi-square tests. Developed a multivariable regression model for VTE on an 80% randomly selected subset of eligible admissions using all measured risk factors for VTE and selected interaction terms. Generalised estimating equations models with a logistic link were used to account for the clustering of patients within hospitals. Initial models were stratified on VTE prophylaxis. Significant factors at p<0.05 were retained. Validation: Internal, split sample. Parameter estimates derived from the model were used to compute individual VTE risk in the remaining 20% of admissions
Number of patients	n= 48, 540

Reference	Rothberg 2011 [279]
Patient characteristics	Age: 18-49 years 12.9%, 50-64 years 21.1%; 65+ years 66.0% Gender (male to female ratio): 41.6 :58.4 Ethnicity: White 64.4%; Black 17.1%; Hispanic 4.1% Primary Diagnosis: Community-Acquired Pneumonia 33.5%; Septicaemia 3.2%; Chronic Obstructive Pulmonary Disease 14.5%; Respiratory Failure 2.8%; Congestive Heart Failure 19.2%; Cardiovascular Disease 13.6%; Urinary Tract Infection 13.1% Any VTE Prophylaxis 29.9% Length of Stay ≥ 6 days 41.1% Paralysis 6.8% Metastatic Cancer 2.2% Solid Tumor Without Metastasis 10.4% Lymphoma 1.2% Cancer Chemotherapy/Radiation 0.5% Prior Venous Thromboembolism 1.2% Oestrogens 2.0% Oestrogen Modulators 0.8% Inflammatory Bowel Disease 0.3% Nephrotic Syndrome 0.2% Myeloproliferative disorder 0.8% Obesity 7.0% Smoking 14.5% Central Venous Catheter 6.3% Inherited or Acquired Thrombophilia 0.0% Steroids 34.2% Mechanical Ventilation 5.5% Urinary Catheter 16.0% Decubitus Ulcer 2.9% Statins Use 23.5%

Reference	Rothberg 2011 [279]
	Use of Restraints 2.5% Diabetes Mellitus 31.1% Varicose Veins 0.1% Hypertension 49.5% Congestive Heart Failure 8.0% Peripheral Vascular Disease 6.7% Valvular Disease 5.6% Pulmonary Circulation Disease 2.3% Chronic Pulmonary Disease 29.7% Respiratory Failure Second Diagnosis 5.5% Rheumatoid Arthritis/Collagen vascular disease 2.9% Deficiency Anaemias 20.2% Setting: 374 acute care facilities Country: USA Inclusion criteria: aged 18 years or over; at moderate to high risk of VTE according to ACCP recommendations; principle diagnosis of pneumonia, heart failure, COPD, stoke, and urinary tract infection. Exclusion criteria: prescribed warfarin or therapeutic dose of heparin on hospital day 1-2; received >1 therapeutic dose of heparin but otherwise did not fulfil criteria for VTE; length of stay <3 days
Target condition(s)	VTE, hospital acquired (3 days after hospitalisation): diagnosis by lower extremity ultrasound, venography, CT angiogram, ventilation-perfusion scan or pulmonary angiogram on hospital day 3 or later; received treatment for VTE at least 50% of the remaining hospital stay; until initiation of warfarin; appearance of a complication (e.g. transfusion or treatment for heparin-induced thrombocytopenia) and were given secondary diagnosis of VTE Prevalence: n= 223 (0.46%)
Risk tool(s)	Unnamed (Rothberg 2011) • No prophylaxis/Any prophylaxis • Gender (male; female) • Length of Stay (< 6 days; ≥ 6 days) • Age (18-49 years; 50-64 years; >65 years)

Reference	**Rothberg 2011** [279]
	• Primary Diagnosis (Pneumonia; Chronic Obstructive Pulmonary Disease; Stroke; Congestive heart failure; Urinary Tract Infection; Respiratory failure; Septicemia) ○ Inflammatory bowel disease ○ Obesity ○ Inherited thrombophelia • Cancer (Cancer 18-49 years; Cancer 50-64 years; Cancer >65 years) ○ Central venous catheter ○ Mechanical ventilation ○ Urinary catheter ○ Chemotherapy ○ Steroids
Statistical measures	Unnamed (Rothberg 2011) • c-statistic 0.75 (0.71 – 0.78)
Source of funding	Not stated
Limitations	Predictors: Unclear if predictor assessments were made without knowledge of outcome data Analysis: No relevant performance measures evaluated Outcome: end point for VTE measurement not stated
Comments	

Reference	**Shaikh 2016** [295]
Study type	Retrospective cohort
Study methodology	Data source: Consecutive patients for reconstructive and body contouring procedures from Jan 2008 to Jan 2012 – retrospective chart review. Validation: External validation
Number of patients	n= 1598
Patient characteristics	Age, mean (range): 49.9 (14-86) years Gender (male to female ratio): 308:1290 Ethnicity: Not reported

Reference	Shaikh 2016 [295]
	BMI, mean (range): 28.2 (15.9-77.5) kg/m^2 Plastic surgery patients: Reconstructive and body contouring procedures including flap-based procedures, removal of facial wrinkles, tissue excision, suction assisted lipectomy, breast prosthesis, and breast reconstruction. Setting: University of Texas Southwestern Medical Centre associated hospitals Country: USA Inclusion criteria: Consecutive patients for reconstructive and body contouring procedures matching Current Procedural Terminology (CPT) codes recorded into original database by the plastic surgery department. Exclusion criteria: Inconsistency in medical records for reporting VTE within 30 days of patient procedure.
Target condition(s)	DVT/PE composite within 30 days of procedure – no further detail given. Prevalence: n= 24 (1.5%)
Risk tool(s)	Caprini Risk Assessment Model • No further tool predictor detail given
Statistical measures	Caprini risk assessment model High risk cut-off 5+ • Sensitivity 0.708 (0.489-0.874) • Specificity 0.394 (0.370-0.419) High risk cut-off 6+ • Sensitivity 0.583 (0.366-0.779) • Specificity 0.601 (0.576-0.625) Highest risk cut-off 9+ • Sensitivity 0.167 (0.05-0.37) • Specificity 0.933 (0.92-0.94)
Source of funding	No funding
Limitations	Outcome: No information on how VTE end point determined. Unclear if recorded without knowledge of risk assessment outcome. Sample size and participant flow: Low event rate compared to the number of predictors in the model

Reference	Shaikh 2016 [295]
	Applicability: US population may differ from NHS population.
Comments	

Reference	Vardi 2013 [327]
Study type	Prospective cohort
Study methodology	Data source: Prospective collection of data through the electronic medical record system. A computerised database was incorporated into the studies electronic medical record system. Physicians were instructed to input pre-determined supplementary data via a mandatory questionnaire that include the structured input of data, alongside automatic data gathering. Also, collected additional data from patients' harts which included information on acute and chronic VTE risk factors and rate of in-hospital. Data collected between 1 February 2008 and 30 April 2009. Validation: Externally validated in a cohort of general internal medicine patients [14]
Number of patients	n=1080
Patient characteristics	Age (mean± SD): 74.68± 16.15; >70: 73.7% Gender (male to female ratio): 1.09:1 Ethnicity: not reported. Condition(s): Patients admitted to internal medicine departments with sepsis. Other relevant characteristics: • Confined to bed: 57.7% • Active cancer: 16.7% • Previous VTE: 5.5% • CHF NYHA 3 or 4: 25.1% • Infectious respiratory diseases: 42.4% • Obstructive respiratory disease: 18.4% • Obesity: 11.8% • Operation within the last 30 days: 1.9% • Varicose veins: 3.1%

Reference	Vardi 2013 [327]
	Setting: 110-bed department of internal medicine in a 450-bed community-based university affiliated hospital Country: Israel Inclusion criteria: Over 18 years old and had a presumed diagnosis compatible with sepsis. Exclusion criteria: No exclusion criteria as stated in the study
Target condition(s)	In hospital VTE (time point: assumption that it is between 48 hours after admission and discharge) Includes DVT and PE. Diagnosis of DVT by Duplex ultrasound or computer tomography (CT) and diagnosis of PE was based on a positive CT angiography (CTA) or a high-probability ventilation perfusion scan. Prevalence: n=14 (1.29%)
Risk tool(s)	Padua Prediction Score A simple score of 11 parameters. The PPS was retrospectively calculated for every patients based on the presence of co-morbidities and clinical presentation. The presence of each medical condition granted cumulative points to the total PPS: • Three points allocated to: Presence of active cancer, previous VTE, reduced mobility, known thrombophilia condition • Two points allocated to: Trauma and/or surgery within the last month • One point allocated to: Elderly age (>70 years), heart failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, obesity, on-going hormonal treatment
Statistical measures	Padua Prediction Score C-statistic: 0.58 (0.43-0.73)
Source of funding	No funding stated
Limitations	Patient selection: Unclear study inclusion and exclusion criteria Sample size and participant flow: There was not a reasonable number of outcome events Analysis: No relevant performance measures evaluated Outcome: unclear timescale for the diagnosis of VTE in patients.
Comments	

Reference	Vaziri 2017 [328]
Study type	Retrospective cohort

Reference	Vaziri 2017 [328]
Study methodology	Data source: Retrospective review of neurosurgical patients treated at the University of Florida between 1 September 2011 and 31 December 2014. Validation: Externally validated in a different surgical populations
Number of patients	n=1006
Patient characteristics	Age: not reported Gender (male to female ratio): 460:546 Ethnicity: not reported. Setting: Single hospital neurosurgical department. Country: United States Inclusion criteria: Patients with either a single neurosurgical CPT code or with two CPT codes in which a secondary CPT code indicated the use of the operating microscope. Exclusion criteria: No exclusion criteria stated in the study
Target condition(s)	VTE (time point: not reported) No details provided. Prevalence: n=13 (1.292%)
Risk tool(s)	American College of Surgeons (ACS) National Surgical Quality Improvement Programme (NSQIP) universal Surgical Risk Calculator No details provided.
Statistical measures	ACS NSQIP universal surgical risk calculator Discrimination: C-statistic: 0.767 Calibration: Intercept 0.361, slope 1.242, p value 0.164
Source of funding	No funding stated
Limitations	Patient selection: Unclear study inclusion and exclusion criteria Predictors: Predictors not presented and unknown if all assessed adequately. Sample size and participant flow: There was not a reasonable number of outcome events Outcome: unclear definition and timescale for the diagnosis of VTE in patients.

Reference	Vaziri 2017 [328]
	Applicability: concerns about predictor definitions and outcome definitions.
Comments	

Reference	Winoker 2017 [340]
Study type	Retrospective cohort
Study methodology	Data source: Random selection of patients from a prospectively maintained multi-institutional database of those treated with robot assisted partial nephrectomy (RAPN) from 2008 to 2016. Validation: Externally validated in a different surgical populations
Number of patients	n=300
Patient characteristics	Age: <65 63.7%; 65-74 26.3%; 75-84 0.3%; ≥ 61.7% Gender (male to female ratio): 185: 115 Ethnicity: not reported. BMI: <18.5 0.7%; 18.5-24.9 13.3%; 25-29.9 39.7%; ≥30 46.3% Setting: Multi-institutional. Country: United States Inclusion criteria: People treated with robot-assisted partial nephrectomy (RAPN) – urological surgery. Exclusion criteria: No exclusion criteria stated in the study
Target condition(s)	VTE (time point: not reported) No details provided. Prevalence: n=1 (0.33%)
Risk tool(s)	American College of Surgeons (ACS) National Surgical Quality Improvement Programme (NSQIP) universal Surgical Risk Calculator No details provided.
Statistical measures	ACS NSQIP universal surgical risk calculator

Reference	Winoker 2017 [340]
	Discrimination: C-statistic: 0.670 Calibration: Brier score 0.003327
Source of funding	No funding stated
Limitations	Patient selection: Unclear study inclusion and exclusion criteria Predictors: Many variables not explicitly known or available in records. Assumptions that all were negative. Sample size and participant flow: There was not a reasonable number of outcome events Outcome: unclear definition and timescale for the diagnosis of VTE in patients. Applicability: concerns about predictor definitions and outcome definitions.
Comments	

Reference	Woller 2011 [342]
Study type	Retrospective cohort
Study methodology	Data source: Data that were collected from the Intermountain Healthcare administrative and electronic medical record (EMR) systems. Admissions occurring from January 1, 2008 and December 31, 2009 served as the validation cohort (The derivation cohort were admissions from January 1,2000 until December 31, 2007) Validation: Internal split sample validation for the Intermountain risk assessment model (Woller 2011) and Kucher Score.
Number of patients	n=46856
Patient characteristics	Age (mean): 61.14 years Gender (male to female ratio): 1.17:1 Ethnicity: not reported Condition(s): Medically ill patients (conditions not reported) Setting: Intermountain Healthcare is a non-profit, university affiliated, integrated health care system with 22 hospitals and more than 150 clinics throughout Utah and South-eastern Idaho. Country:

Reference	Woller 2011 [342]
	Inclusion criteria: Hospital admissions involving adult patients (≥ 18 years) admitted to an Intermountain Healthcare medicine inpatient service. Patients were defined as medicine patients if they were admitted to internal medicine or medical subspecialties Exclusion criteria: Patients admitted to the hospital with a primary admission diagnosis code for VTE
Target condition(s)	VTE (90 days) (not defined) Prevalence: n= 2109 (4.5%)
Risk tool(s)	Intermountain risk assessment model Risk factors included in the RAM are: • Prior VTE • An order for bed rest • PICC insertion • Diagnosis of cancer The number of points allocated to each risk factor was not reported. Unclear what score = at risk. Kucher Score • Three points allocated to: cancer, prior VTE, hypercoagulability • Two points allocated to: major surgery • One point allocated to: bed rest, age > 70 years, obesity (BMI > 30), hormone replacement therapy/oral contraceptives
Statistical measures	Intermountain risk assessment model • C-statistic – 0.843 (0.833-0.852) Kucher Score • C-statistic – 0.756 (0.746-0.767) • C – statistic for published bimodal cut-off with a score being ≥4 – 0.683
Source of funding	Grant provided by the Deseret Foundation
Limitations	Analysis: No relevant performance measures evaluated Outcome: no definition for the target condition of VTE is reported
Comments	

H.1.2 Hospital admissions

Reference	Hostler 2016 [150]
Study type	Prospective data collection with retrospective record review for analysis.
Study methodology	Recruitment: prospectively collected characteristics on admission and VTE prophylaxis data each hospital day for all consecutive adult patients (≥18 years) admitted for a medical illness to the Walter Reed Army Medical Hospital over an 18-month admission period (Sept 2009 through March 2011). Validation: External validation of the IMPROVE BRS in a large group of hospitalised patients.
Number of patients	n=1668 (1294 admitted to a medical ward + 374 admitted to a medical ICU or cardiac care unit who met IMPROVE criteria) 12327 patient admissions → 10594 excluded due to surgical diagnoses, hospital days <3, paediatrics, trauma, behavioural health, bleeding diagnoses, VTE, Tx dose anticoagulations → 1733 individual record search → 65 excluded due to surgery, VTE or Tx anticoagulation dose.
Patient characteristics	Age: <40: 234 (14%), 40-84: 1144 (68.6%), ≥85: 289 (17.3%) Gender (male to female ratio): 969:699 Ethnicity: not reported <u>Medical conditions</u> Bleeding within 3 months: 3.2% Active gastroduodenal ulcer: 2% Platelets < 50 x 10^9 cells/L: 2.7% Hepatic failure, INR > 1.5: 5.7% ICU/CCU: 22.4% Central venous catheter: 17.8% Current cancer: 21.6% GFR ≥ 60 mL/min/m^2: 64.3% Rheumatic diseases: 1.6% Heart failure: 8.9% Thrombophilia: 0.5% Previous VTE: 6.1%

Reference	Hostler 2016 [150]
	Aspirin during admission: 37.1% <u>Bleeding</u> n= 45 (31 major, 14 clinically relevant non-major) GI origin: n=18 No readily identifiable source: n=11 Haematuria: n=4 Postoperative: n=4 Intracerebral haemorrhage: n=2 Intra-abdonimal haematoma: n=2 Vascular injuries: n=2 Haemothorax: n=1 Retinal haemorrhage: n=1 <u>IMPROVE scores</u> <7: 78% (n=1301 calculated based on % reported) ≥7: 22% (n=367 calculated based on % reported) <u>IMPROVE score + bleeding</u> <7 group 1.6% major bleeding 2.7% clinically important bleeding ≥7 group 5.4% major bleeding 6.5% clinically important bleeding <u>Chemical prophylaxis</u> n=726 (43.5%) receiving low-molecular-weight heparin (LMWH) n=509 (30.5%) receiving unfractioned heparin (UFH)

Reference	Hostler 2016 [150]
	n=8 (0.5%) receiving fondaparinux n=336 (20%) no chemoprophylaxis Setting: Walter Reed Army Medical Hospital Country: USA Inclusion criteria: 18 years or over admitted to hospital (the general medical wards and in the ICU) with a medical illness. Exclusion criteria: All patients on the database who did not meet the inclusion criteria used by the IMPROVE investigators. Patients were excluded if they were admitted for bleeding or if they were receiving treatment-dose anticoagulation on admission or during the hospitalisation.
Target condition(s)	Major bleeding (30 days): Inpatient and outpatient electronic medical records for new bleeding diagnoses that occurred during hospital stays and within 30 days of discharge. Used International Classification of Disease (ICD-9): 578.0 (hematemesis, vomiting blood), 578.1 (blood in stool), 578.9 (haemorrhage of GI tract unspecified), 459.0 (haemorrhage unspecified), 430 (subarachnoid haemorrhage), 431 (intracerebral haemorrhage), 432.0 (non-traumatic extradural haemorrhage), 432.1 (subdural haemorrhage), 432.9 (unspecified intracranial haemorrhage); and a haematocrit drop > 6 points to identify patients who may have bled during admission. All bleeding events were confirmed by manual chart audit. Bleeds were defined as major or clinically relevant non-major using the criteria outlined by the IMPROVE investigators and the International Society on Thrombosis and Haemostasis guidelines. Combined and referred to as "clinically important" bleeds. Minor bleeding events not assessed.
Risk tool(s)	<u>The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) bleeding risk score (BRS)</u> No further description provided. IMPROVE BRS score for each patient calculated using admission data and medical record review to identify bleeding events. Details of IMPROVE BRS from derivation study[80] **Factor (points/weighting)** 1. Gastro-duodenal ulcer (4.5) 2. Bleeding prior 3 months (4) 3. Admission platelets <50x109 (4) 4. Hepatic failure (2.5) 5. ICU/CCU stay (2.5) 6. CV catheter (2) 7. Rheumatic diseases (2) 8. Current cancer (2)

Reference	Hostler 2016 [150]
	9. Sex [M vs F] (1) 10. Age ≥ 85 years vs <40 years (3.5) 11. Age 40-84 vs <40 years (1.5) 12. Severe renal failure GFR <30 vs ≥60 mL/min/m^2 (2.5) 13. Moderate renal failure 30-59 vs ≥60 mL/min/m^2 (1) Author suggested cut-off: use caution in prescribing anticoagulant prophylaxis to patients with an admission bleeding risk score of ≥7
Statistical measures	<u>IMPROVE RBS</u> Predicting major bleeding at 14 days[a] TP 11 FP 266 FN 12 TN 961 Sensitivity 48% (27, 69) Specificity 78% (76, 81) AUC (95% CI): 0.64 (0.57-0.77) *p*=0.008 Predicting bleeding throughout hospitalisation[a] TP 15 FP 266 FN 16 TN 961 Sensitivity 48% (30, 67) Specificity 78% (76, 81) Predicting clinically important bleeding at 14 days AUC (95% CI): 0.64 (0.55-0.73) *p*=0.006
Source of funding	None reported
Limitations	• Risk of bias: Unclear if outcome determined without knowledge of the predictor information; Number of events less than 10 x the number of predictors in the model; unclear if all participants included in analysis as different number reported throughout the paper with bleeding events and IMPROVE score ≥7; No discrimination or calibration data reported (AUC only). • Indirectness: no serious indirectness

Reference	Hostler 2016 [150]
Comments	

a) Raw data for 2x2 tables provided by author correspondence

H.1.3 Risk assessment tools in patients admitted to hospital

Study	Cassidy 2014[43]
Study type	Before and after study
Number of studies (number of participants)	1 (n=1569)
Countries and setting	Conducted in USA; Setting: Boston Medical Center (BMC) is a merged entity of the former Boston University Hospital and Boston City Hospital, with 509 licensed bed.
Line of therapy	Not applicable
Duration of study	Other: Before implementation: 2009; Post-implementation: July 2011-June 2012
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: National Surgical Quality Improvement Program (NSQIP) defines DVT as a new diagnosis of venous thrombosis, confirmed by imaging study or autopsy, which is treated with anticoagulation or placement of vena cava filter. PE is defined as a new diagnosis of a new blood clot in a pulmonary artery, which is confirmed by imaging or autopsy.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients who underwent an operation on the general and vascular surgery services at the institution during the specified time periods, and who were accrued to the NSQIP database, including those admitted to an ICU or to a non-ICU.
Exclusion criteria	Not reported
Recruitment/selection of patients	National Surgical Quality Improvement Program (NSPQIP) data for patients in the institution.
Age, gender and ethnicity	Age: Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Indirectness of population	Serious indirectness – US population
Interventions	(n=1569) Intervention 1: No risk tool. Before development of the standardised program, no VTE prevention guidelines

	were formally used. Surgeons generally acknowledged the American College of Chest Physicians guidelines, but no structured system existed and no individualised risk stratification was performed. There were no electronic reminders about VTE prophylaxis, and no surgeons used the Caprini system to guide decisions. Duration 2009. Concurrent medication/care: Pre-intervention analysis of practice revealed that patients generally remained in bed more than desired. In order to understand baseline care of post-operative patients at their institution before development of the VTE prevention program, they audited mobilisation practices in the spring of 2010. All patients who had undergone elective open abdominal or pelvic operations were visited at 8:00 AM, 1:00 PM and 6:00 PM on the day of surgery and during the 2 subsequent days. Nurses were unaware of these audits. Trained clinical staff recorded whether each patient was in bed, sitting in a chair or walking at the time of the visit. Audits were observational only and were not intended to directly alter patient management. Pre-intervention analysis revealed that patients generally remained in bed more than desired. Mobilisation orders were often absent or vague, e.g. orders might have simply stated “ambulate” without specifying a frequency and nurses were not required to document details about ambulation. Mobilisation program was fully implemented in August 2010, and further audits were performed between 8 and 14 weeks after implementation. (n=1323) Intervention 2: Risk tool. Developed a scoring system for VTE risk assessment and integrated it into the electronic inpatient medical record. The system uses a check-box format so that each risk factor is explicitly listed and may be selected with a simple click. The risk score is calculated based on the selected factors, and the patient is placed into 1 of 5 risk categories (lowest: Caprini score = 0; low: Caprini score = 1-2; moderate: Caprini score = 3-4; high: Caprini score = 5-8 or highest risk: Caprini score = > 9). Electronic order system is customised to require that a Caprini score be calculated for every patient at the time of operation and/or admission within general surgery and vascular surgery standardised order sets. If the surgery team does not calculate the Caprini score and act on the electronic recommendations, the orders cannot be completed. Therefore, they made an effort to ensure that each patient would be scored according to the Caprini model. Standardised VTE prophylaxis regimens were created and linked to Caprini risk categories. The prophylaxis regimens provide the recommended mechanical and pharmacological prophylaxis along with suggested duration. The electronic order system was designed to require that all patients received standardised prophylaxis regimens. Electronic reminders are used for prophylaxis to encourage adherence to a standardised prevention strategy. Caprini Risk Tool. Score 1:• Age 41-59 (years)• Abnormal pulmonary function• Acute myocardial infarction (<1 month)• BMI ≥30 (kg/m2)• Congestive heart failure (<1 month)• History of inflammatory bowel disease• History of prior major surgery (<1 month)• Sepsis (<1 month)• Serious acute lung disease (<1 month)• Swollen legs (current)• Varicose veins• Minor surgery planned• Medical patient currently on bed rest• Leg plaster cast or brace• Central venous access. Score 2:• Age 60-74 (years)• Major surgery (> 60 minutes)• Previous malignancy• Arthroscopic surgery (>60 minutes)• Laparoscopic surgery (>60 minutes)• Morbid obesity (BMI> 40 kg/m2)Score 3:• Age ≥75 (years)• History of SVT, DVT/PE• Family history of VTE• Present cancer or chemotherapy• Positive anticardiolipin antibody• Positive Lupus anticoagulant• Acute spinal cord injury (<1 month)• Major surgery (2-3 hours)• BMI > 50 kg/m2 (venous stasis syndrome)• Congenital thrombophilia: positive factor V Leiden, positive prothrombin 20210A, elevated serum homocysteine• Acquired thrombophilia: positive lupus anticoagulant, elevated anticardiolipin antibodies, HIT• Other

	thrombophilia Score 5:• Elective major lower extremity athroplasty• Hip, pelvis or leg fracture (<1 month)• Stroke (<1 month)• Multiple trauma (<1 month)• Acute spinal cord injury (paralysis) (<1 month)• Major surgery >3 hours. Duration July 2011 to June 2012. Concurrent medication/care: Increased level of adherence to recommended prophylaxis regimens after implementation of the electronic risk-stratification and prophylaxis program. Adherence to the recommended prophylaxis and duration was 77% for patients in the highest risk category. Standardised VTE prophylaxis regimens and linked them to the Caprini risk categories, the surgeon may decline VTE prophylaxis when it is contrary to his or her judgement by choosing the "opt out" selection in the order sets. This prompts an automatic drop-down menu that indicates reasons for not prescribing VTE chemoprophylaxis including active bleeding, heparin allergy, or contraindication. Combined the requirement for Caprini risk stratification and commensurate prophylaxis with a standardised post-operative mobilisation program. Created specific standardised mobilisation instructions and included them in order sets used for all general surgery and vascular surgery patients. The nursing orders require that each patient be out of bed at least 3 times daily, beginning on the day of the operation. Nurse educators and surgeons met with unit nurses, including those from the ICU to review baseline outcomes data and to establish expectations for mobilisation, program was implemented in August 2010.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RISK TOOL - BEFORE IMPLEMENTATION versus RISK TOOL - AFTER IMPLEMENTATION Protocol outcome 1: DVT (calculated from percentage reported in paper) - Actual outcome: DVT at 30 days; Group 1: 30/1569, Group 2: 4/1323; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: PE (calculated from percentage reported in paper) - Actual outcome: PE at 30 days; Group 1: 17/1569, Group 2: 7/1323; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	VTE (symptomatic or asymptomatic) (up to 90 days from hospital discharge); Fatal PE (up to 90 days from hospital discharge); Major bleeding (up to 90 days from hospital discharge); Quality of life (up to 90 days from hospital discharge); All-cause mortality at (up to 90 days from hospital discharge); Fatal bleeding (up to 90 days from hospital discharge) ; Length of hospital stay (up to 90 days from hospital discharge); Unplanned hospital readmission (up to 90 days from hospital discharge); Haemorrhagic stroke (up to 90 days from hospital discharge); Heparin-induced thrombocytopenia (up to 90 days from hospital discharge)

Study	**Catterick 2014[44]**
Study type	Before and after study

Number of studies (number of participants)	(n=not reported, data reported as per 100,000)
Countries and setting	Conducted in United Kingdom; Setting: 152 hospital trusts, England
Line of therapy	Not applicable
Duration of study	Intervention time: Data from 2006/7 to 2011/12
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ICD-10 codes used by the UK All Party Parliamentary Thrombosis Group
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Recruitment/selection of patients	Obtained monthly secondary diagnoses, 30-day, 60-day and 90-day readmissions, and admissions data from the Health and Social Care Information Centre as Hospital Episode Statistics at NHS hospital trust level, from financial years 2006-2007 to 2011-2012. Readmission analyses were based on data from 152 hospital trusts in England. General mortality and population data from the Office of National Statistics.
Age, gender and ethnicity	Age: Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	(n=100000) Intervention 1: Risk tool. Department of Health risk assessment tool Review the patient-related factors shown on the assessment sheet against thrombosis risk, ticking each box that applies (more than one box can be ticked).Any tick for thrombosis risk should prompt thromboprophylaxis according to NICE guidance. The risk factors identified are not exhaustive. Clinicians may consider additional risks in individual patients and offer thromboprophylaxis as appropriate. Risk factors in the tool are: - Surgical patient- Medical patient expected to have ongoing reduced mobility relative to normal state- Medical patient NOT expected to have significantly reduced mobility relative to normal state- Active cancer or cancer treatment- Significantly reduced mobility for 3 days or more- Age > 60- Hip or knee replacement- Dehydration- Hip fracture- Known thrombophilias- Total anaesthetic + surgical time > 90 minutes- Obesity (BMI >30 kg/m2)- Surgery involving pelvis or lower limb with a total anaesthetic + surgical time > 60 minutes- One or more significant medical comorbidities (eg heart disease ;metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)- Acute surgical admission with inflammatory or intra-abdominal condition- Personal history or first-degree relative with a history of VTE- Critical care admission- Use of hormone replacement therapy- Surgery with significant reduction in mobility- Use of oestrogen-containing contraceptive therapy- Varicose veins with phlebitis- Pregnancy or < 6 weeks post-partum (see NICE guidance for specific risk factors)- Active bleeding- Neurosurgery, spinal surgery or eye surgery- Acquired bleeding disorders (such as acute liver failure)- Other procedure with high bleeding risk- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with

	INR >2)- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours- Acute stroke- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours- Thrombocytopaenia (platelets< 75x109/l)- Uncontrolled systolic hypertension (230/120 mmHg or higher)- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease). Duration 2010/11 (after implementation). Concurrent medication/care: n/a (n=100000) Intervention 2: No risk tool. Details about practice prior to implementation not reported. Duration 2009 (before implementation). Concurrent medication/care: n/a
Funding	Primary author paid student internship at Sanofi, UK during the study period
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RISK TOOL - BEFORE IMPLEMENTATION versus RISK TOOL - AFTER IMPLEMENTATION Protocol outcome 1: All-cause mortality (up to 90 days from hospital discharge) - Actual outcome: VTE-related mortality at 90 days (time-point provided by author); Group 1: mean: 9.8395 per 100000, Group 2: mean: 9.0059 per 100000; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Unplanned hospital readmission (up to 90 days from hospital discharge) - Actual outcome: VTE-related readmission at 30 days; Group 1: mean: 126.5443 per 100000, Group 2: mean: 124.9660 per 100000; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: VTE-related readmission at 90 days; Group 1: 189.6489 per 100000, Group 2: 193.9462 per 100000; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	DVT (up to 90 days from hospital discharge); PE (up to 90 days from hospital discharge); Fatal PE (up to 90 days from hospital discharge); Major bleeding (up to 90 days from hospital discharge); Quality of life (up to 90 days from hospital discharge); Fatal bleeding (up to 90 days from hospital discharge); Length of hospital stay (up to 90 days from hospital discharge); Haemorrhagic stroke (up to 90 days from hospital discharge); Heparin-induced thrombocytopenia (up to 90 days from hospital discharge)

Study	**Germini 2016[119]**
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=628)
Countries and setting	Conducted in Italy; Setting: Two internal medicine sections of the University Hospital of Perugia

Line of therapy	1st line
Duration of study	Intervention time: During hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	General medical: Hospitalised acutely ill medical patients.
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years or older admitted to internal medicine.
Exclusion criteria	Expected hospital stay <48 hours, any indication for anticoagulant therapy, recent (within 2 weeks) or active major bleeding, platelet count lower than 100 x 109/L, creatinine clearance lower than 30 mL/min, and pregnancy.
Recruitment/selection of patients	Consecutive admissions from December 2012 to March 2014
Age, gender and ethnicity	Age - Median (IQR): Risk tool 75.1 (62.8, 81.5); no tool 72.4 (59.8, 80.5). Gender (M:F): 340/288. Ethnicity:
Further population details	High risk (PPS ≥4): PPS 32.7%; clinical judgment 39.4% Given prophylaxis: PPS 15.3%; clinical judgment 12.2% Of those at low risk (PPS<4) prophylaxis not given: PPS 94.9%; clinical judgment 96.2%
Indirectness of population	No indirectness
Interventions	(n=298) Intervention 1: Risk tool. Padua prediction score - all patients admitted to Section 1 Internal Medicine were allocated to PPS-based strategy. Physicians working in Section 1 were trained to use the PPS and a tool for PPS calculation was added to the section medical charts. Antithrombotic prophylaxis was suggested in patients with PPS score ≥4. Duration During hospital stay. Concurrent medication/care: None stated. Indirectness: No indirectness. (n=515) Intervention 2: No risk tool. No risk tool - all patients admitted to Section 2 Internal Medicine were allocated to clinical judgment-based strategy. The decision to prescribe antithrombotic prophylaxis was left to the attending physician and no specific training was performed. Duration During hospital stay. Concurrent medication/care: None stated. Indirectness: No indirectness
Funding	Funding not stated (None reported)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RISK TOOL versus NO RISK TOOL

Protocol outcome 1: DVT at 90 days
- Actual outcome for General medical: Symptomatic and asymptomatic DVT including proximal or distal. Complete compression ultrasonography of the lower limbs at

discharge of in case of clinical suspicion of VTE. at During hospital stay; Group 1: 20/235, Group 2: 61/393 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: PPS group more likely to have a recent trauma or surgery. Clinical judgment group more likely to be affected by stroke. ; Group 1 Number missing: 63, Reason: No echo performed; Group 2 Number missing: 122, Reason: No echo performed Protocol outcome 2: PE at 90 days - Actual outcome for General medical: Pulmonary embolism confirmed by CT angiography or V/Q lung scanning at During hospital stay; Group 1: 1/235, Group 2: 0/393 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: PPS group more likely to have a recent trauma or surgery. Clinical judgment group more likely to be affected by stroke. ; Group 1 Number missing: 63, Reason: No echo performed; Group 2 Number missing: 122, Reason: No echo performed Protocol outcome 3: Fatal PE at 90 days - Actual outcome for General medical: Fatal PE at During hospital stay; Group 1: 1/235, Group 2: 0/393 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: PPS group more likely to have a recent trauma or surgery. Clinical judgment group more likely to be affected by stroke. ; Group 1 Number missing: 63, Reason: No echo performed; Group 2 Number missing: 122, Reason: No echo performed Protocol outcome 4: Major bleeding at 90 days - Actual outcome for General medical: Major bleeding - unclear definition at During hospital stay; Group 1: 0/235, Group 2: 2/393 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Very high, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: No definition of major bleeding offered. Unclear how similar to review protocol outcome definition. ; Baseline details: PPS group more likely to have a recent trauma or surgery. Clinical judgment group more likely to be affected by stroke. ; Group 1 Number missing: 63, Reason: No echo performed; Group 2 Number missing: 122, Reason: No echo performed Protocol outcome 5: All cause mortality at 90 days - Actual outcome for General medical: Death at During hospital stay; Group 1: 4/235, Group 2: 6/393 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: PPS group more likely to have a recent trauma or surgery. Clinical judgment group more likely to be affected by stroke. ; Group 1 Number missing: 63, Reason: No echo performed; Group 2 Number missing: 122, Reason: No echo performed
Protocol outcomes not reported by the study	VTE at 90 days; Quality of life at 90 days; Fatal bleeding at 90 days; Length of hospital stay at 90 days; Unplanned hospital readmission at 90 days; Post-thrombotic syndrome at 90 days; Pulmonary hypertension at 90 days; Haemorrhagic stroke at 90 days; Heparin-induced thrombocytopenia at 90 days

Study	Lester 2013[205]
Study type	Retrospective cohort study
Number of studies (number of participants)	(n=Unclear)
Countries and setting	Conducted in United Kingdom; Setting: N/A
Line of therapy	Not applicable
Duration of study	Intervention time: 21 months (July 2010-March 2012)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ICD10 codes - specified by the NHS-Outcome Framework 2013/14: I260, I269, I800, I801, I802, I803, I808, I809, I821, I822, I823, I829, O082, O223, O229, O870, O871, O879, O882
Stratum	Split surgical/non-surgical patients
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients admitted to NHS hospitals
Exclusion criteria	Not reported
Recruitment/selection of patients	Data from 163 English NHS hospitals. Patient admissions placed in four different categories. 1) Non-surgical admissions >3 days 2) Non-surgical admissions <4 days 3) Surgical admissions >3 days 4) Surgical admissions <4 days
Age, gender and ethnicity	Age: Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	(n=17712681) Intervention 1: Risk tool – start of implementation. Use of Department of Health risk assessment tool in achieving ≥90% VTE risk assessment. Department of Health risk assessment tool - Review the patient-related factors shown on the assessment sheet against thrombosis risk, ticking each box that applies (more than one box can be ticked).Any tick for thrombosis risk should prompt thromboprophylaxis according to NICE guidance. The risk factors identified are not exhaustive. Clinicians may consider additional risks in individual patients and offer thromboprophylaxis as appropriate. Risk factors in the tool are: - Surgical patient- Medical patient expected to have ongoing reduced mobility relative to normal state- Medical patient NOT expected to have significantly reduced mobility relative to normal state- Active cancer or cancer treatment- Significantly reduced mobility for 3 days or more- Age > 60- Hip or knee replacement- Dehydration- Hip fracture- Known thrombophilias- Total anaesthetic + surgical time > 90 minutes- Obesity (BMI >30 kg/m2)- Surgery involving pelvis or lower limb with a total anaesthetic + surgical time > 60 minutes- One or more significant medical comorbidities (eg heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)- Acute surgical admission with inflammatory or intra-abdominal condition- Personal history or first-degree relative with a history of VTE- Critical care admission- Use of hormone replacement therapy- Surgery with significant reduction in mobility- Use of oestrogen-containing contraceptive therapy- Varicose

	veins with phlebitis- Pregnancy or < 6 weeks post-partum- Active bleeding- Neurosurgery, spinal surgery or eye surgery- Acquired bleeding disorders (such as acute liver failure)- Other procedure with high bleeding risk- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR >2)- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours- Acute stroke- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours- Thrombocytopaenia (platelets< 75x109/l)- Uncontrolled systolic hypertension (230/120 mmHg or higher)- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease). Duration July 2010. Concurrent medication/care: N/A (n=17712681) Intervention 2: Risk tool – after implementation. Use of Department of Health risk assessment tool in achieving ≥90% VTE risk assessment. Duration March 2012. Concurrent medication/care: N/A
Funding	Academic or government funding (Funded solely by University Hospital Birmingham NHS Foundation Trust)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RISK TOOL - START OF IMPLEMENTATION OF DOH TOOL versus RISK TOOL - AFTER IMPLEMENTATION OF DOH TOOL

Protocol outcome 1: All-cause mortality (up to 90 days from hospital discharge)
- Actual outcome: Non-surgical admissions >3 days: VTE-related mortality post-discharge at 90 days; RR 0.963 (95%CI 0.814 to 1.138) (p-value 0.653); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Non-surgical admissions <4 days: VTE-related mortality post-discharge at 90 days; RR 0.743 (95%CI 0.602 to 0.918) (p-value 0.006); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Surgical admissions >3 days: VTE-related mortality post-discharge at 90 days; RR 0.816 (95%CI 0.646 to 1.031) (p-value 0.088); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Surgical admissions <4 days: VTE-related mortality post-discharge at 90 days; RR 0.730 (95%CI 0.459 to 1.162) (p-value 0.184); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Non-surgical admissions >3 days: Primary VTE-related mortality post-discharge at 90 days; RR 0.886 (95%CI 0.714 to 1.099) (p-value 0.269); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Non-surgical admissions <4 days: Primary VTE-related mortality post-discharge at 90 days; RR 0.617 (95%CI 0.472 to 0.808) (p-value 0.001); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Surgical admissions <4 days: Primary VTE-related mortality post-discharge at 90 days; RR 0.568 (95%CI 0.303 to 1.067) (p-value 0.078); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Surgical admissions >3 days: Primary VTE-related mortality post-discharge at 90 days; RR 0.624 (95%CI 0.44 to 0.884) (p-value 0.008); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	VTE (symptomatic or asymptomatic) (up to 90 days from hospital discharge); DVT (symptomatic or asymptomatic) (up to 90 days from hospital discharge); PE (up to 90 days from hospital discharge); Fatal PE (up to 90 days from hospital discharge) ; Major bleeding (up to 90 days from hospital discharge); Quality of life (up to 90 days from hospital discharge); Fatal bleeding (up to 90 days from hospital discharge) ; Length of hospital stay (up to 90 days from hospital discharge); Unplanned hospital readmission (up to 90 days from hospital discharge); Haemorrhagic stroke (up to 90 days from hospital discharge); Heparin-induced thrombocytopenia at 90 days (up to 90 days from hospital discharge)

Study	**Roberts 2013[274]**
Study type	Before and after study
Number of studies (number of participants)	(n=302057)
Countries and setting	Conducted in United Kingdom; Setting: King's College Hospital located in south London. 900-bed tertiary referral centre which also provides secondary care for the local population with > 150,000 admissions each year.
Line of therapy	Not applicable
Duration of study	Intervention time: 2010 (April 2010-March 2011) and 2011 (April 2011-March 2012)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hospital associated thrombosis (HAT): any new episode of VTE, diagnosed during hospitalisation or within 90 days of discharge following an inpatient stay of at least 2 days, or a surgical procedure under general or regional anaesthesia. VTE diagnoses were identified by the thrombosis team from screening radiology reports of CT pulmonary angiogram, ventilation/perfusion scans, upper and lower limb venous compression ultrasound, primary or secondary discharge diagnoses of VTE identified from ICD10 codes I80.0-80.9, I26.0-26.9 or O22.2, O22.3, O87.0 or O87.1, post-mortem reports, and death certificates with VTE listed as a primary cause of death.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged > 18 years
Exclusion criteria	Not reported
Recruitment/selection of patients	Confirmed diagnoses of VTE in adults (>18 years of age) were cross-referenced with electronic patient records to identify HTA
Age, gender and ethnicity	Age: Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Indirectness of population	No indirectness

Interventions	(n=302057) Intervention 1: Risk tool. Department of Health risk assessment tool - Review the patient-related factors shown on the assessment sheet against thrombosis risk, ticking each box that applies (more than one box can be ticked).Any tick for thrombosis risk should prompt thromboprophylaxis according to NICE guidance. The risk factors identified are not exhaustive. Clinicians may consider additional risks in individual patients and offer thromboprophylaxis as appropriate. Risk factors in the tool are: - Surgical patient- Medical patient expected to have ongoing reduced mobility relative to normal state- Medical patient NOT expected to have significantly reduced mobility relative to normal state- Active cancer or cancer treatment- Significantly reduced mobility for 3 days or more- Age > 60- Hip or knee replacement- Dehydration- Hip fracture- Known thrombophilias- Total anaesthetic + surgical time > 90 minutes- Obesity (BMI >30 kg/m2)- Surgery involving pelvis or lower limb with a total anaesthetic + surgical time > 60 minutes- One or more significant medical comorbidities (eg heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)- Acute surgical admission with inflammatory or intra-abdominal condition- Personal history or first-degree relative with a history of VTE- Critical care admission- Use of hormone replacement therapy- Surgery with significant reduction in mobility- Use of oestrogen-containing contraceptive therapy- Varicose veins with phlebitis- Pregnancy or < 6 weeks post-partum (see NICE guidance for specific risk factors)- Active bleeding- Neurosurgery, spinal surgery or eye surgery- Acquired bleeding disorders (such as acute liver failure)- Other procedure with high bleeding risk- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR >2)- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours- Acute stroke- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours- Thrombocytopaenia (platelets< 75x109/l)- Uncontrolled systolic hypertension (230/120 mmHg or higher)- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease). Duration 2010 (April 2010-March 2011). Concurrent medication/care: A number of strategies were used to facilitate adoption of the VTE risk assessment tool, including the establishment of a network of VTE link nurses and midwives to ensure local expertise and leadership within each ward area. Mandatory VTE training was provided to all clinical staff (nurses, doctors, pharmacists). Engaging clinical staff with the VTE prevention process required multiple tailored approaches, e.g. education regarding patient safety and the role of thromboprophylaxis. A prompted mandatory electronic risk assessment was introduced in 2011 across all inpatient areas expect day surgery, intensive care and obstetrics. Completion of the risk assessment was linked to thromboprophylaxis guidance. (n=302057) Intervention 2: Risk tool. Use of Department of Health risk tool to achieve sustained improvement in risk assessment on the incidence of VTE and the proportion of events attributable to inadequate prophylaxis The cut-point for comparison was delayed for 3 months following achievement of 90% risk assessment to account for potential lag in outcome improvement and the definition of VTE, including events occurring up to 90 days post-discharge. Duration 2011 (April 2011-March 2012). Concurrent medication/care: n/a
Funding	No funding received

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RISK TOOL - BEFORE DOH versus RISK TOOL - AFTER DOH RISK TOOL Protocol outcome 1: VTE (up to 90 days from hospital discharge) - Actual outcome: Hospital associated thrombosis (HAT) - VTE at 90 days; RR 0.88 (95%CI 0.79 to 0.98) (p-value 0.014); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: DVT (up to 90 days from hospital discharge) - Actual outcome: DVT at 90 days; RR 0.95 (95%CI 0.83 to 1.09); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: PE at 90 days (up to 90 days from hospital discharge) - Actual outcome: PE at 90 days; RR 0.79 (95%CI 0.67 to 0.94) (p-value 0.004); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Fatal PE at 90 days (up to 90 days from hospital discharge); Major bleeding (up to 90 days from hospital discharge); Quality of life (up to 90 days from hospital discharge); Fatal bleeding (up to 90 days from hospital discharge) ; Length of hospital stay (up to 90 days from hospital discharge); Unplanned hospital readmission (up to 90 days from hospital discharge); Haemorrhagic stroke (up to 90 days from hospital discharge); Heparin-induced thrombocytopenia at 90 days (up to 90 days from hospital discharge)

H.2 Risk assessment for people having day procedures

H.2.1 VTE day procedures

Reference	**Ay 2010[10]**
Study type	Prospective cohort
Study methodology	Data source: patients enrolled between October 2003 and December 2008 in CATS study Validation: split sample validation (Khorana 2008[171])
Number of patients	n= 819
Patient	Age: median 62 (25^{th}-75^{th} percentile 53 – 68)

Reference	Ay 2010[10]
characteristics	Gender (male to female ratio): 56:44 Ethnicity: not reported <u>Site of cancer, n (%)</u> Breast 140 (17.1) Lung 125 (15.3) Stomach 36 (4.4) Colorectal 112 (13.7) Pancreas 47 (5.7) Kidney 24 (2.9) Prostate 112 (13.7) Brain (high-grade glioma) 108 (13.1) Lymphoma 97 (11.8) Multiple myeloma 18 (2.2) <u>Cancer treatment during observation period, n (%)</u> Chemotherapy 537 (65.6) Surgery 334 (40.8) Radiotherapy 396 (48.4) <u>Combination of treatments during observation period, n (%)</u> Chemo- and radiotherapy 153 (18.7) Chemotherapy and surgery 85 (10.4) Surgery and radiotherapy 73 (8.9) Chemotherapy, surgery and radiotherapy 102 (12.5) Median body mass index, kg/m² (25th-75th percentile) 25.0 (22.3-28.1) Setting: Medical University of Vienna Country: Austria

Reference	Ay 2010[10]
	Inclusion criteria: (1) patients with newly diagnosed cancer of the brain, breast, lung, upper or lower gastrointestinal tract, pancreas, kidney, prostate or gynecologic system; sarcoma; hematologic malignancies (myeloma, high- and low-grade lymphoma); or progression of disease after complete or partial remission; (2) histologic confirmation of diagnosis; (3) age more than 18 years; (4) willingness to participate; and (5) written informed consent Exclusion criteria: overt bacterial or viral infection within the last 2 weeks, venous or arterial thromboembolism within the last 3 months, and continuous anticoagulation with vitamin K antagonists or low molecular weight heparin (LMWH); surgery or radiotherapy within the last 2 weeks and chemotherapy within the last 3 months to exclude a transient influence of these interventions on the hemostatic system
Target condition(s)	VTE (180 days): no routine screening for VTE. When a patient developed symptoms of VTE, objective imaging methods were performed to confirm or exclude the diagnosis. Duplex sonography or venography were applied for diagnosis of deep vein thrombosis (DVT) and computerized tomography or ventilation/perfusion lung scan for diagnosis of pulmonary embolism (PE) Prevalence of VTE: n= 61 (7.4%)
Risk tool(s)	Khorana score Two points allocated to: • Very high risk (stomach, pancreas) One point allocated to: • High risk (lung, lymphoma, gynaecologic, bladder, testicular) • Pre-chemotherapy platelet count 350 x 109/L or more • Haemoglobin level less than 100 g/L or use of red cell growth factors • Pre-chemotherapy leukocyte count more than 11 x 109/L • BMI 35 kg/m2 or more Population divided into 3 risk categories based on the score from the risk model • Low (score 0) • Intermediate (score 1-2) • High (score≥3)
Statistical measures	Khorana score (≥3) Sensitivity: 31.9% Specificity: 91.9% PPV 22.1%

Reference	Ay 2010[10]
	NPV 94.9%
Source of funding	grant from the Jubilaumsfonds of the Austrian National Bank (project numbers 10935 and 12739); unrestricted grant from Pfizer Austria
Limitations	Risk of bias: risk of bias in outcome reporting as there was no routine screening for VTE, screening only conducted when patients developed symptoms of VTE; there was not a reasonable number of outcome events Indirectness: no serious indirectness
Comments	

Reference	Bezan 2017 [29]
Study type	Retrospective cohort
Study methodology	Data source: Consecutive patients with testicular germ cell tumours (TGCT) across all clinical stages treated at a single University Hospital between January 2003 and December 2013. Validation: External validation
Number of patients	n= 349
Patient characteristics	Age, median: 34.9 years Gender: not reported Ethnicity: not reported <u>Histology</u> Seminoma 56.8% Non-seminoma 43.2% <u>Clinical tumour stage</u> Stage IA-B 64.8% Stage IS 2.6% Stage II1-IIC 14.3% Stage IIIA-C 18.3% <u>Prophylaxis</u>

Reference	Bezan 2017 [29]
	n=7 (2%) with LMWH for the duration of chemotherapy. Prescribed at individual physician's discretion. Setting: Two university hospitals. Country: Austria (derivation), Switzerland (Validation) Inclusion criteria: Not reported. Exclusion criteria: Not reported.
Target condition(s)	VTE (12 months) Prevalence of VTE: n= 18 (5.2%)
Risk tool(s)	Unnamed (Bezan 2017) Predictive model based on tumour stage and a large retroperitoneal lymphadenopathy (RPLN). VTE risk stratification rule with the following four categories: • cSIA-B (VTE 12 month risk 1.7%) • cS IS-IIB (5.9%) • cS IIC (14.3%) • cS IIIA-C (21.4%) Patients with cS IIC and cS III disease have a very high risk of VTE and may benefite from primary prophylaxis for the duration of chemotherapy.
Statistical measures	C-statistic: 0.84
Source of funding	No funding.
Limitations	Risk of bias: Unclear inclusion and exclusion criteria, model weighting unclear, unclear time interval between assessment of predictors and determination of outcome. Insufficient performance measures reported – no sensitivity and specificity. Indirectness: VTE not defined, unclear determination for all participants.
Comments	

Reference	Cella 2017 [45]
Study type	Prospective cohort with risk tool assessed retrospectively
Study methodology	Data source: patients with active cancers enrolled between October 2012 and April 2014. Validation: External validation

Reference	Cella 2017 [45]
Number of patients	n= 843
Patient characteristics	Age: not reported Gender: Female 66.4% Ethnicity: not reported <u>Primary tumour site</u> Breast 36.6% Gastroenteropancreatic 30% Genito/urinary tract 12.9% Lung 4% Metastatic patients 55.2% Other (kidney, neuroendocrine tumours, head and neck, sarcoma, GIST, hepatocellular carcinoma, skin, brain) 16.5% Patients undergoing chemotherapy 87.2% Setting: Federico II University of Naples and the University Cancer Centre Leipzig. Country: Italy and Germany Inclusion criteria: Patients ≥18 years with a diagnosis of solid tumours confirmed by cytology/histology at any stage and candidate to received chemotherapy, endocrine therapy, radiotherapy, target therapy, and/or surgery, alone or in combination and with at least 6 months life expectation. Exclusion criteria: end-stage renal or liver disease and disease-free patients.
Target condition(s)	VTE (12 months): symptomatic and asymptomatic. Confirmed by Doppler ultrasound and CT Prevalence of VTE: n= 73 (8.6%)
Risk tool(s)	<u>Khorana Score</u> *Score 2* Very high-risk tumour (stomach pancreas) *Score 1* High-risk tumour (lung, gynaecological, genitourinary excluding prostate) Hemoglobin level <100 g/L or use of red cell growth factors

Reference	Cella 2017 [45]
	Prechemotherapy leukocyte count >11 x 10^9/L Prechemotherapy platelet count 350 x 10^9/L or greater BMI 35 or greater Calculated on 96.4% (n=813) of population: • >2 High-risk – 56 (6.9%); with VTE events 45 (6.1%) • 1-2 Intermediate risk – 352 (43.3%); with VTE events 30 (41.1%) • 0 Low risk – 405 (49.8%); with VTE events 32 (43.8%)
Statistical measures	Khorana score Sensitivity and specificity calculated using the risk stratification and prevalence data presented in Table 4 based on high-risk cut-off • Sensitivity 15% (8-25) • Specificity 94% (92-96) C-statistic: 0.583
Source of funding	None reported
Limitations	Risk of bias: Unclear if predictors assessed without knowledge of outcome and vice versa. Not all patients had Khorana score calculated (n=30) Indirectness: No indirectness
Comments	

Reference	Khorana 2008[171]
Study type	Prospective cohort
Study methodology	Data source: The study population comprised consecutively enrolled patients in the Awareness of Neutropenia in Chemotherapy (ANC) Study Group Registry, an observational study of cancer patients initiating a new chemotherapy regimen. Patients were followed prospectively for a maximum of 4 cycles of chemotherapy. Patients enrolled between March 2002 and October 2005 who had completed at least one cycle were included in the analysis. Validation: Internal split sample validation
Number of patients	n= 1365
Patient	Age: <65 years 62.3%; ≥65 years 37.7%

Reference	Khorana 2008[171]
characteristics	Gender (male to female ratio): 1:2 Ethnicity: not reported Cancer patients undergoing chemotherapy <u>Primary site of cancer:</u> Breast – 34.6% Colorectal – 11.9% Lung – 17.3% Gynaecologic – 10.40% Gastric and pancreatic 1.4% Lymphoma – 13.5% Other sites – 10.9% <u>Stage of cancer:</u> 1 to 3 – 64% 4 – 34.9% Unknown – 1.1% Setting: 115 sites within the United States Country: USA Inclusion criteria: People were required to have a histologically confirmed diagnosis of cancer, with targeted enrolment of specific tumour types (breast, lung, ovarian, sarcoma, colon and lymphomas), eligible patients with other primary sites were allowed on the study. Patients were required to be at the start of a new chemotherapy regimen, expected to complete 4 cycles of chemotherapy, be aged 18 years or older with no upper age limit, and to provide informed consent Exclusion criteria: People who were receiving concurrent cytotoxic, biologic, or immunologic therapy for other conditions, or continuous single-agent chemotherapy, if they had a diagnosis of acute leukaemia, were pregnant or lactating, had an active infection requiring treatment, were currently participating in a double-blinded study, or had received stem cell transplant were excluded.
Target condition(s)	VTE (time point and definition unclear) Prevalence of VTE: n= 28 (2.1%)

Reference	Khorana 2008[171]
Risk tool(s)	Unnamed (Khorana 2008) Predictive model based on risk factors/patient characteristics for chemotherapy associated VTE Two points allocated to: • Very high risk (stomach, pancreas) One point allocated to: • High risk (lung, lymphoma, gynaecologic, bladder, testicular) • Pre-chemotherapy platelet count 350 x 10^9/L or more • Haemoglobin level less than 100 g/L or use of red cell growth factors • Pre-chemotherapy leukocyte count more than 11 x 10^9/L • BMI 35 kg/m^2 or more • Population divided into 3 risk categories based on the score from the risk model • Low (score 0) • Intermediate (score 1-2) • High (score≥3)
Statistical measures	Sensitivity: 35.7% Specificity: 89.6% PPV: 6.7% NPV: 98.5% C-statistic: 0.70 Hosmer-Lemeshow test p=0.15
Source of funding	Supported by a Career Development Award to primary author from the National Cancer Institute. The Awareness of Neutropenia in Chemotherapy (ANC) Study Group received research grant support from Amgen for the development of the patient registry. Secondary author supported by a National Institutes of Health grant.
Limitations	Risk of bias: Sample size and participant flow: there was not a reasonable number of outcome events, unclear time between predictor assessment and outcome assessment Indirectness: VTE not defined and timepoint unclear
Comments	

Reference	Pannucci 2012[254]
Study type	Prospective cohort
Study methodology	Data source: The American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) database from 2005-2009 was used. All adult patients whose surgery was listed as outpatient and who had a length of stay equal to zero days were included for analysis in the ACS-NSQIP Patient Use File. Validation: Internal split validation
Number of patients	n= 85,730
Patient characteristics	Age: <40 years 19.28%, 40-60 years 39.59%, 61-74 years 28.4%, 75+ years 12.73% Gender (male to female ratio): 1:1.4 Ethnicity: not reported Outpatient surgical patients: Integument: 22% Musculoskeletal: 9.1% Respiratory and cardiovascular: 0.1% Arteries and veins: 6.4% Hemic and lymphatic system, mediastinum and diaphragm: 0.9% Head and neck, oesophagus: 1.5% Foregut (stomach, including gastric bypass procedure): 1.6% Hindgut (small bowel, large bowel, rectum and anus): 4.7% Liver, biliary system, and pancreas: 13% Miscellaneous peritoneal procedures: 0.9% Herniorrphaphy:33% Urinary system: 1.2% Genital system (male or female): 2% Endocrine: 3.0% Nervous system structures: 0.5% Setting: Not reported

Reference	Pannucci 2012[254]
	Country: USA Inclusion criteria: Patients who had outpatient surgery or surgery with subsequent 23-hour observation Exclusion criteria: Not reported
Target condition(s)	VTE (30 days): DVT and/or PE. DVT is considered to be a new thrombus within the venous system that is confirmed using an objective imaging method (e.g. duplex ultrasound or computed tomography scan). PE is defined as an obstructing thrombus within the pulmonary arterial system. PE requires confirmation using an objective imaging method (e.g. computed tomography scan or arteriogram Prevalence of DVT: n= 87 (0.10%) Prevalence of PE: n=37 (0.043%)
Risk tool(s)	Unnamed (Pannucci 2012) • Two point allocated to: Age 40-59, OR time ≥ 120 minutes, BMI ≥ 40 • Three points allocated to: age ≥ 60 • Five points allocated to: active cancer • Six points allocated to: athroscopic surgery • Eight points allocated to: current pregnancy • Ten points allocated to: sapheno-femoral junction surgery • Eleven points allocated to: Non-GSV venous surgery If patients have a total score of: • 0-2 - classified as low risk level • 3-5 - classified as moderate risk level • 6-10 - classified as high risk level • ≥ 11 - classified as highest risk level
Statistical measures	C-statistic: 0.78 (0.7212 - 0.8388). Confidence intervals calculated from standard error (SE ± 0.03) Hosmer-Lemeshow test p=0.826
Source of funding	Dr. Pannucci (primary author) receives salary support through a NIH grant
Limitations	Risk of bias: not all relevant performance measures evaluated
Comments	

Reference	van Es 2017 [324]
Study type	Prospective cohort
Study methodology	Data source: Multinational cohort recruited between July 2008 and February 2016. Validation: External validation
Number of patients	n= 876
Patient characteristics	Age, mean (SD): 64 (11) years Gender: 59% male Ethnicity: not reported BMI, mean (SD): 25 (4) <u>Tumour type</u> Lung 26% Oesophagus 19% Colorectal 18% Pancreas 12% Breast 9% Prostate 5% Gastric 5% Ovarian 5% Bladder 1% Distant metastases 66% Setting: Seven hospitals in four countries Country: The Netherlands, Italy, France and Mexico All included patients did not receive routine thromboprophylaxis in accordance with current guidelines.

Reference	van Es 2017 [324]
	Inclusion criteria: Outpatients with lung, oesophageal, colorectal, pancreatic, breast, prostate, gastric, ovarian or bladder cancer classified as stage III or IV according to the American Joint Committee on Cancer criteria if they were scheduled for chemotherapy within 7 days or had started chemotherapy in the previous 3 months. Exclusion criteria: Current prophylactic or therapeutic anticoagulation or adjuvant chemotherapy.
Target condition(s)	VTE (180 days, 6 months) Composite of objectively confirmed symptomatic or incidental PE, distal or proximal leg DVT, or non-catheter-related upper extremity DVT, or symptomatic catheter-related upper extremity DVT. Patients did not undergo screening. Prevalence: n= 53 (6.1%)
Risk tool(s)	Khorana Score *Score 2* Pancreatic or gastric cancer *Score 1* Lung, ovarian or bladder cancer Hemoglobin level <10 g/dL or use of erythropoietin stimulating agents Prechemotherapy white blood cell count >11 x 10^9/L Prechemotherapy platelet count ≥350 x 10^9/L BMI >35 kg/m^2
Statistical measures	C-statistic: 0.52 (0.47-0.58)
Source of funding	Unrestricted grants from participating hospitals
Limitations	Risk of bias: Unclear handling of n=33 cases with missing data. Unclear when predictor information calculated. Not all relevant performance measures evaluated (no sensitivity and specificity provided and insufficient data reported to calculate).
Comments	

Reference	Wang 2017 [331]
Study type	Retrospective cohort
Study methodology	Data source: Electronic medical records of Hepatocellular Carcinoma (HCC) patients who presented at a single hospital between January 2000 to July 2015 using ICD-9 codes for malignant neoplasm of liver and intrahepatic biliary duct. Validation: External validation

Reference	Wang 2017 [331]
Number of patients	n=270
Patient characteristics	Age, mean (range): 58.5 (26-80) Gender (M/F): 50/220 Ethnicity: not reported HCC with Barcelona stage 0-A 42.6% Advanced HCC with Barcelona stage C or D 57.4% Chemotherapy: n=91 (33.7%) Setting: Cook County Health and Hospital System, Chicago. Country: USA Inclusion criteria: Reviewed and selected patients if they had histopathology-proven or radiographically proved HCC by triple-phase enhanced CT and/or MRI of the abdomen. Exclusion criteria: Incomplete data, less than 18 years, had prior VTE to the diagnosis of HCC, incomplete follow-up of less than 1 month in the institution.
Target condition(s)	VTE (symptomatic). Diagnosed based on radiographic examinations using compression ultrasound, contrast-enhanced CT, and pulmonary angiogram. No systemic VTE screening. Prevalence: n=16 (5.93%)
Risk tool(s)	Khorana Score *Score 2* Pancreatic or gastric cancer *Score 1* Lung, ovarian or bladder cancer Hemoglobin level <10 g/dL or use of erythropoietin stimulating agents Prechemotherapy white blood cell count >11 x 10^9/L Prechemotherapy platelet count ≥350 x 10^9/L BMI >35 kg/m^2

Reference	Wang 2017 [331]
	Calculated based on the information collected at time of diagnosis. High risk ≥3 – 2 (0.7%) Intermediate risk 1-2 – 84 (31.1%) Low risk 0 – 184 (68.1%)
Statistical measures	Sensitivity and specificity calculated from data in Table 2 page 3. • Sensitivity 0% • Specificity 99.2%
Source of funding	No financial support
Limitations	Risk of bias: Unclear if predictors assessed without knowledge of outcome data and vice versa. Unclear time interval. There are not a reasonable number of outcome events in comparison to number of predictors in the model. Analyses only presented for one threshold that is not the usual one. VTE time point assessment unclear. Indirectness: no indirectness
Comments	

H.2.2 Major bleeding day procedures

No relevant studies were identified.

H.2.3 Risk assessment tools in patients who are having day procedures (including surgery and chemotherapy) at hospital

No relevant studies were identified.

H.3 Reassessment

H.3.1 Reassessment of people who are admitted to hospital

No relevant studies were identified.

H.3.2 Reassessment of people who are having day procedures at hospital

No relevant studies were identified.

H.4 Risk assessment for pregnant women and women up to 6 weeks postpartum

Reference	Sultan 2016 [308]
Study type	Retrospective cohort (registry data)
Study methodology	Data source: The Swedish national inpatient register (IPR) and the Swedish Medical Birth Registry (SBR) for information on pregnancies in women with no history of venous thromboembolism resulting in a live birth or stillbirth between 1 July 2005 and 31 December 2011. Derivation: Records from England based Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES). Validation: The information provided her is the first external validation.
Number of patients	n=498918 women with 662,387 deliveries
Patient characteristics	Age: mean (SD) 30.32 (5.23) Ethnicity: not reported Mean BMI (SD): 24.62 (4.57) – 8.6% missing pre-pregnancy BMI information. Varicose veins – 0.78% heart disease – 0.77% Kidney disease – 1.01% Inflammatory bowel disease – 0.80% Pre-eclampsia/eclampsia – 3.63% Diabetes – 2.26%

Reference	Sultan 2016 [308]
	Hypertension – 1.20% Nulliparous – 44.26% Para 1 – 36.59% Para 2 – 13.41% Para ≥3 – 5.75% Preterm birth (<37 weeks) – 4.79% Postpartum haemorrhage – 7.30% Spontaneous/assisted vaginal delivery 82.68% Elective caesarean – 8.76% Emergency caesarean – 8.56% Multiple delivery (twins or more) – 1.41% Stillbirth – 0.35% Puerperal acute infection – 7.30% Infant's mean (SD) birth weight – 3519.80 (581.90) grams Postpartum venous thromboembolism: 521 women (absolute rate of 7.9 per 10,000 deliveries). Setting: Swedish Registry Country: Sweden Inclusion criteria: Women with no history of venous thromboembolism resulting in a live birth or stillbirth between 1 July 2005 and 31 December 2011. Exclusion criteria: None reported.
Target condition(s)	Postpartum VTE: Occurrence of a first venous thromboembolism (deep vein thrombosis or pulmonary embolism) within the first six weeks after delivery. The algorithm used to define a valid VTE was accompanied by a prescription for an anticoagulant within 90 days of the event or if the patient died within 30 days of the event.
Risk tool(s)	Risk prediction model Risk score from a logistic regression model to predict venous thromboembolism in the first six weeks postpartum. Risk score =-9.103+0.94x(0.227*smoker*+1.221*varicose veins*+0.848*comorbidities (cardiac, renal, or inflammatory bowel disease)*+0.721*pre-eclampsia/eclampsia*+0.421*diabetes*+0.502*postpartum haemorrhage*+1.151*stillbirth*+1.097*postpartum infection*+(0.750*emergency section/*0.563*elective section*)+(0.165*parity of 1*/0.481*parity of 2*/0.566*parity of ≥3*)-0.0000798*age at delivery*^{3} + 0.0000214 (*age at delivery*^{3} log (*age at delivery*))+0.00026641*BMI*^{3}-0.0000650(*BMI*^{3} log (*BMI*))-22156315*infant birth weight*$^{-2}$+3455223.4(*infant birth weight*$^{-2}$ log (*baby's birth*

Reference	Sultan 2016 [308]
	weight)). All variables are coded as binary (0 or 1 for absence or presence of a risk factor), except for age, BMI, and birth weight. These variables were transformed on the basis of fractional polynomial regression analysis. The value -9.103 is the intercept, and the other numbers are the estimated regression coefficients for the predictors, which indicate their mutually adjusted relative contribution to the outcome risk. The regression coefficients represent the log odds ratio for a change of 1 unit in the corresponding predictor. The predicted risk of VTE=1/1+$e^{-riskscore}$ log=natural logarithm In the development of this model primary candidate predictors were selected from the most recent version of the RCOG thromboprohylaxis guideline and additional predictors were added based on previous studies of important obstetric risk factors for VTE.
Statistical measures	<u>Risk prediction model</u> • C-statistic – 0.73(0.71-0.0.75) • Calibration slope – 1.11 (1.01-1.20) Top 1% risk score cut-off (threshold 41.2) – arbitrary threshold • Sensitivity 9.0% (6.7-11.8) • Specificity 99.0% (98.9-99.0) • PPV 0.71 (0.52-0.94) Top 5% risk score cut-off (threshold 19.7) – arbitrary threshold • Sensitivity 26.7% (22.9-30.7) • Specificity 95.0% (95.0-95.1) • PPV 0.41 (0.35-0.50) Top 6% cut-off (threshold = 18 per 10,000 deliveries) – based on number of pregnant women warranting thromboprophylaxis based on old Swedish guidelines • Sensitivity 30.3% (26.4-34.5) • Specificity 93.8% (93.7-93.9) • PPV 0.38 Top 10% risk score cut-off (threshold 14.0) – arbitrary threshold • Sensitivity 35.5% (31.4-40.0) • Specificity 90.0% (90.0-90.1) • PPV 0.27 (0.24-0.32)

Reference	Sultan 2016 [308]
	Top 20% risk score cut-off (threshold 9.8) – arbitrary threshold • Sensitivity 53.4% (50.0-57.7) • Specificity 80.0% (79.9-80.1) • PPV 0.21 (0.18-0.23) Top 25% risk score cut-off (threshold 8.7) – arbitrary threshold • Sensitivity 59.5% (55.1-63.7) • Specificity 75% (74.9-75.1) • PPV 0.19 (0.16-0.21) Top 35% cut-off (threshold = 7.2 per 10,000 deliveries) – based on number of pregnant women warranting thromboprophylaxis based on old UK guidelines • Sensitivity 68.1% (63.9-72.1) • Specificity 65.1% (64.9-65.2) • PPV 0.15
Source of funding	Funded by University of Nottingham/Nottingham University Hospital's NHSD Trust senior clinical research fellowship and by the Swedish Research Council (project number 2013-2429).
Limitations	Predictors: unclear if predictor assessments made without knowledge of outcome data. Similarly whether outcome determined without knowledge of predictor information. Unclear time interval between predictor assessment and outcome determination. Analysis: Thresholds not pre-specified for sensitivity and specificity ratings.
Comments	

H.5 Giving information to patients and planning for discharge (qualitative evidence)

Study	Apenteng 2016
Aim	To examine patients' understanding of hospital-associated thrombosis and their experience with thromboprophylaxis
Population	Patients who were classed by hospital staff as being at high risk of developing VTE during a recent hospital admission

Study	Apenteng 2016
	n=31; Male: 54.8%, Female 45.2%; 9.7% aged ≤40 years, 35.5% aged 41-64 years, 38.7% aged 65-74 years, 12.9% aged ≥75 years, 12.9% unknown. 58.1% orthopaedic surgery, 22.6% gastrointestinal surgery, 19.3% other surgery. AES only 16.1%, injectable prophylaxis only 6.5%, both AES and injectable prophylaxis 77.4%.
Setting	Interviews took place in the patients' homes
Study design	In person semi-structured interviews
Methods and analysis	Purposeful sampling was employed to select interview participants of maximum variety of age, gender, condition requiring hospital stay and site. Semi-structured interviews were used. These lasted between 10-45 minutes and were conducted in person at the patients' homes. The interviews were guided by a topic guide that comprised open ended questions that drew reflections on patients' recent hospital admissions. All interviews were audio recorded and transcribed verbatim. Data collection continued until theoretical saturation was attained. Three researchers read through the interview transcripts to familiarise themselves with the interviews and identify emerging themes. They met to compared, discuss and finalise themes for the coding frame. Based on this, one of the researchers coded the remaining interviews which were analysed using framework analysis.
Findings	**Theme 1. Awareness of VTE risk.** Patients were aware or the risk of blood clots although did not specifically refer to the terms DVT and PE. Those having orthopaedic surgery described having a discussion of the risks including blood clots, whereas other surgical patients did not report the same level of discussion. Patients' information came from information given during their work up or from previous personal experience or experience of family members. Many patients were not aware that they had a VTE risk assessment and assumed prophylaxis was a normal part of treatment.
	Theme 2. Experience of VTE prophylaxis. Patients reported mixed views on self-injecting and also reported differing levels of guidance provided on the injections. Some received training whereas others reported much less instruction. Despite this, all patients reported completing the course of injections. Most participants understood that injections were to prevent blood clots, although some demonstrated limited understanding of the rationale. Participants reported a great deal of inconsistency in terms of administration of AES and a lack of clarity on the use of AES. Adherence of AES was low, with reasons for this cited as lack of guidance, and discomfort. Participants also reported conflicting information regarding AES from nurses, doctors, and information leaflets, making it difficult for participants to know the correct course of action.
	Theme 3. Knowledge of VTE symptoms. Many participants reported that they did not think they would recognise the symptoms of a blood clot, whereas other participants could describe vague symptoms relating to DVT. There was a lack of awareness of the symptoms associated with PE, with only two participants describing PE related symptoms.
	Theme 4. Post discharge support. Many participants did not think it necessary to routinely activate GP involvement post discharge, and all reported that they had coped fine with the current system. Patients felt that they would be able to contact their GP if they did have any concerns
	Theme 5. Perceived gap in patient education. Patients reported that they would value more education in VTE, particularly in terms of how VTE prophylaxis works, clarity on AES use and some information on symptoms in order to recognise if they were having a blood clot. It was felt that it may also be useful to be warned about possible side effects of prophylaxis and some touched on the lack of public awareness and the potential need for a public health campaign.

Study	Apenteng 2016
Limitations and applicability of evidence	The researchers followed clear methods, although the justification of some of these methods is not clear, and the description of the data analysis methods is only briefly described. The aims and context of the research is clearly outlined and the data is rich and relevant to the aim of the study. There was no explicit mention of reflexivity. The researchers did not detail their professional backgrounds or provide insight into how this may have influenced the interview and analysis process The aim of the study is directly relevant to our review protocol and the population of both orthopaedic and non-orthopaedic surgical patients means that this evidence is applicable to the review question.

Study	May 2006
Aim	To explore patient experiences of AES, to ascertain their perception about their use and care and to identify any limitations in the information currently provided to inform the design of a patient information leaflet
Population	People who had been patients in hospital within the last two months and who had worn compression stockings for a period of 48 hours or more n=12; Thigh length AES 9, knee length AES 3
Setting	East Kent, UK
Study design	Telephone semi-structured interviews
Methods and analysis	Researchers gave patients who were interested a brief verbal introduction, consent forms and paid return envelopes. Written project information was sent to potential participants, written and verbal consent was obtained. Semi-structured interviews with 12 participants were used. An interview schedule with open ended questions which had been piloted in two subjects was used to guide the interviews. Telephone interviews were taped and transcribed, and a copy was sent to the participants to check for accuracy. Each researcher (eight members) individually analysed transcripts for emerging themes and consensus was obtained through discussion. Theme saturation was obtained in a sample of 12 patients
Findings	**Theme 1. Amount and type of information received**. Most patients could not remember receiving information regarding everyday care of AES. Some patients recalled having an information leaflet but remembered very little of what it said.
	Theme 2. Amount and type of information desired. Some patients perceived that nursed would have supplied necessary information. One participant thought that that in a hospital, "you do as you are told". Some did not think that information is required and viewed it as common sense, while others thought that it is nice to have a leaflet to read and it would have been helpful to have some information in the hospital.
	Theme 3. Previous experience/secondary knowledge. Most patients had little alternative source of information other than that acquired in the hospital. The other sources were included health information from long haul flights and previous experience with VTE – either self or family.

Study	May 2006
	Theme 4. Reasons for wearing AES. Not all patients understood the reason to wear GCS. Some understood that it was meant to stop the blood from clotting and prevent DVT, but some could not relate this to their situation since they did not have DVT. Some patients who did not understand fully thought that AES were "given to you for a reason", but it can be taken off if you can't wear them after trying them on.
	Theme 5. Experiences with AES fitting and use/lack of information. • There was a lack of information about how to put on and take off the AES, or how it should fit. Some patients obtained the information from other patients, family and friends or other health care professionals, and this resulted in a variety method which may not be appropriate. • Confusing or lack of information on duration of the AES, when to take them off/change them off, particularly whether to stop wearing them or continue wearing them at home. • Most patients did not receive information about how to take AES off and wash them, resulting them relying on "common sense" and many used inappropriate methods. • Lack of information given about prophylactic exercises.
Limitations and applicability of evidence	The was a lack of information given about the data analysis methods used. The researchers did reported the interview schedule and reported rich and relevant data. No explicit statement of reflexivity was made. The population and research aim was relevant to the review question and the evidence is applicable. The themes are relevant and are useful in addressing our question.

Study	Najafzadeh 2015
Aim	To explore patients' perceptions and understanding in regard to the benefits and risks of antithrombotic therapy for the prevention of VTE after a joint replacement surgery
Population	Patients who had undergone hip or knee replacement surgery at a tertiary care hospital (Brigham and Women's Hospital, Boston, MA) between January and June 2014 and who were 18 years of age or older n=12; Male: 25%, Female 75%; 33%aged 18–65 years, 25% 65–69 years, 17% 70-75 years, 8% 75-80 years, 17% ≥80 years. 75% hip replacement, 25% knee replacement. Heparin 8%, warfarin 75 %, unnamed oral antithrombotic medication 17%.
Setting	Interviews took place at the tertiary care hospital or over the phone
Study design	In person or phone semi-structured interviews

Study	Najafzadeh 2015
Methods and analysis	Semi-structured interviews were used. These lasted 30 minutes, and were conducted in person at the tertiary care hospital for five participants and over the phone for seven participants. The interviews were guided by a list of questions designed to address the study objective. In particular, participants were asked whether they were aware and had a clear understanding of potential complications that might occur following the surgical procedure e.g. DVT and PE, in contrast with unrelated but possibly more familiar conditions e.g. stroke and myocardial infarction; whether they knew about the benefits and risks of using 'blood thinners'; and what factors affected their decisions to comply with (or not comply with) prophylactic antithrombotic treatment. Additionally, participants and the interviewer had the opportunity to discuss issues that they deemed to be relevant to the study topic as they emerged during the interviews. Interviews were recorded, transcribed and analysed using the constant comparative method. Transcripts were initially reviewed with the aim of developing an overall understanding of the scope and content of data. Issues requiring further clarification were then identified, which were included as discussion topics in the subsequent interviews. Subsequently, a line-by-line analysis of transcripts was conducted and codes were assigned to phrases and sentences as a concept became apparent. The appropriateness of code assignments was assessed by reviewing the previously coded data and ascertaining consistent assignment of codes to concepts. As more data were reviewed, the code structure was modified inductively by refining existing codes and adding new codes when necessary. Data were hand coded and reviewed separately by two investigators to identity major themes and concepts. All discrepancies were resolved by discussion.
Findings	**Theme 1. Patients' understanding of VTE.** 67% of participants stated that they were informed about potential complications, 50% had a clear understanding of DVT and 42% had a clear understanding of PE. In contrast, all participants had a basic understanding of stroke and MI.
	Theme 2. Patients' perceptions about the benefits of antithrombotic therapy. Nearly all participants (92%) were aware of benefits of antithrombotic therapy, describing a reduction in the risk of blood clot formation after surgery by thinning the blood. However some participants (58%) assumed that it could also reduce the risk of stroke and MI.
	Theme 3. Patients' perceptions about the risks of antithrombotic therapy. Participants mentioned the risk of excess bleeding in case of injury and bruising as a possible side effect of treatment, however only half considered the risk of major bleeding events. Participants described the risk of bleeding associated with antithrombotic therapy as a consequence of their blood becoming too thin, and half acknowledged serious bleeding as a possible side effect.
	Theme 4. Factors influencing patients' decision to use antithrombotic medications. Participants reported trusting their physician's expertise as a primary reason for their decision to use antithrombotic medication as prescribed. Participants perceived bleeding as an event that could be monitored, controlled and reversed, and therefore as having less severe consequences compared to clots. Most participants were willing to trade off an increased risk of bleeding for a reduced VTE risk. Those that did report legitimate concerns about bleeding risk (family bleeding history, bleeding disorder) did not discuss these with their doctors and assumed that there was no other option, and that their physician had carefully considered their individual profile to assure benefits outweighed risks.
Limitations and applicability of evidence	The researchers followed clear methods to ensure the validity and rigour of their qualitative analysis. However of note is that there was no explicit mention of reflexivity. The researchers did not detail their professional backgrounds or provide insight into how this may have influenced the interview and analysis process

Study	Najafzadeh 2015
	The inclusion of questions that relate to our review protocol, and a research aim clearly in line with the current topic, makes this evidence applicable to the review question. Although the study focus is quite narrow, the themes are relevant and are useful in addressing our question.

Study	Noble 2006
Aim	To find out what in patients with advanced cancer who are receiving palliative care think about the effect of thromboprophylaxis on overall quality of life
Population	Patients who had metastatic cancer or primary brain tumour with no curative treatment available n=28; age range 53-76; type of cancer breast 7, prostate 3, lung 3, unknown 3, ovarian 3, colon 4, pancreatic 3, brain 1, uterine 1
Setting	Specialist palliative care unit within the regional cancer centre (Cardiff), which had established thromboprophylaxis guidelines.
Study design	Semi-structured interviews
Methods and analysis	Semi-structured interviews were used. These were audio taped and then transcribed, and covered the following topics: cancer treatments received (such as surgery, chemotherapy, and radiotherapy); insight into prognosis; what was understood about treatment with low molecular weight heparin and thromboprophylaxis; the impact of thromboprophylaxis on overall quality of life; negative aspects of being on heparin treatment A thematic analysis was employed, using an inductive approach to obtain categories emerging from the data. Patients recruited until theoretical saturation (when no further recurring themes emerged from analysis) was achieved.
Findings	**Theme 1. Knowledge and understanding**. All patients understood the purpose of heparin and many understood why they were at risk; immobility and surgery were identified as risk factors. All patients knew death is a consequence, but unaware of DVT symptoms such as painful swollen legs, or of pulmonary embolism, such as dyspnoea. Most knowledge was based on media coverage and association with long haul flights, but there was little understanding of the specific association with cancer.
	Theme 2. Acceptability. All patients found thromboprophylaxis with LMWH acceptable, and many could not understand why it would be considered unacceptable. Patients recognised that thromboprophylaxis with heparin was part of usual practice and described it as a reassurance that something is being done for them. They considered treatment with heparin was neither pleasant nor unpleasant, and balanced benefits against side effects.
	Theme 3. Reassurance and optimism. Patients understood that they had a terminal illness but expressed a desire to optimise quality of life not only by treating symptoms but also by taking measures to prevent other symptoms. Thromboprophylaxis with heparin reassured most patients that something was being done to prevent other problems and that the medical team had not given up on them.
	Theme 4. Views and concerns about thromboprophylaxis methods and side effects

Study	Noble 2006
	• Bruising: Bruising was the only negative experiences reported from LMWH but that did not seem to be a big concern/bother, especially when compared with the treatments and side effects experienced for cancer. • Discomfort from AES: Several patients had worn AES during previous hospital admissions and all had found them uncomfortable (hot, itchy and tight), and not acceptable for long term wear
	Theme 5. Terminally ill patients wish to be involved in decision making about thromboprophylaxis. Patients expressed their need to be involved in decision making, particularly with respect to the withdrawal or non-administration of treatment.
Limitations and applicability of evidence	The researchers provide limited information about the questions and probes used during the interviews, and how the analysis was conducted. There was a lack of reflexive statement, exploring the role of the researchers background and experience an how this may have influenced the interview and analysis. The inclusion of questions that relate to our review protocol, and a research aim clearly in line with the current topic, makes this evidence applicable to the review question. The study focus is quite narrow, concentrating on a distinct population which is a small sub-set of the population of interest in the protocol.

H.6 General VTE prevention for everyone in hospital

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Barker and Hollingsworth, 2004[15]	Survey	3	**Total:** 218	**Type of surgery:** Mixed surgical patients from 16 wards in one hospital	**Type:** Graduated compression stockings (GCS) Survey of concordance with hospital policy of wearing thigh-length	**Not applicable** **Additional non-comparative prophylaxis:** Not reported	1 day	**No of patients wearing GCS in accordance with hospital policy**	9/218 (4%)	The 5/14 wearing thigh high GCS incorrectly had them rolled down to below the knee. This leads to graduated compression loss and a constriction band formed by the rolled down
								No of patients wearing any GCS	99/218 (46%)	
								No of patients wearing thigh GCS	14/99 (14%)	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
					stockings after surgery. **Additional non-comparative prophylaxis:** Not reported			**No of patients wearing thigh GCS correctly**	9/14 (64%)	band. Staff not routinely offering thigh high stockings.
								No of patients wearing below knee GCS	85/99 (86%)	
								No of patients wearing below knee GCS correctly	77/85 (91%)	

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Benko et al., 2001[20]	Patient views of interventions from RCT	3	**Total**: 200 5 randomised groups: 2 brands of thigh-length stockings with 40 patients in each arm 2 brands of knee-length stockings with 40 patients in each arm 1 group of no intervention.	**Type of surgery:** Orthopaedic patients	**Type:** Thigh-length graduated compression stockings (GCS) n = 80 2 brands of thigh-length, 40 in each group **Additional non-comparative prophylaxis:** Not reported	**Type:** Below knee graduated compression stockings n = 80 2 brands of thigh-length, 40 in each group **Additional non-comparative prophylaxis:** Not reported	1 hour	**No. patients with wrinkles in stockings after 1 hour**	**Int:** 14/80 **Cont:** 6/80 **p value:** <0.05	Main aim was to investigate the difference in venous haemodynamics in inpatients prior to surgery. Only results for patient views reported here.
								No. patients reporting discomfort after 1 hour	**Int:** 17/80 **Cont:** 9/80 **p value:** <0.05	
								No. patients unable to manage stockings independently	**Int:** 38/80 **Cont:** 44/80 **p value:** >0.1	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Brady et al., 2007[34] **Study design:** Observational **Evidence level:** + **Duration of follow-up:** Short term prophylaxis	**Patient group:** Nursing care patients in teaching hospital with orders for TEDS &/or SCD **Setting:** Teaching hospital, California, from autumn 2003 to winter 2005 **Inclusion criteria:** ▪ Randomly selected patients with orders for thromboembolic deterrent stockings (TEDS) and/or sequential compression device (SCD) admitted to any of these nursing units(neurological, transplantation, vascular, gastrointestinal; ear nose and throat, internal medicine, trauma and orthopaedics) **Exclusion criteria** ▪ Patients who did not have sufficient stamina or mental clarity to complete the 15-minute survey, or restrained patients. ▪ <18 years old	TEDS &/or SCD **Types of SCDs used[#]:** ▪ Thigh length: 70/137 (51%) ▪ Knee length: 46/137 (34%) ▪ Unsure: 22/137(16%) **Types of TEDs used:** ▪ Thigh length: 82/137 (60%)[#] ▪ Knee length: 41/137(30%) ▪ Unsure: 14/137 (10%) **Methods:** A survey of patient view on the following ▪ why stockings/SCDs were being used ▪ Comfort ▪ How long they wore per day Observations on the fit of TEDs and/or SCDs. Survey content and observational descriptors determined based on literature review and clinical observations made by nurses.	**Correlation between gender and compliance** **Correlation between age and compliance** **Observation of SCD usage at time of survey**	No correlation found. R values not reported Pearson r =0.247, p<0.01 (older patients more consistent in wearing stockings/SCD) **Wearing[#]:** 40/137 (29.2%) **SCDs in room, but not using:** 65/137 (47%) **No SCDs visible in room:** 26/137 (19%) **Thigh length:** **Wearing:** 21/70 (30%) **Appropriate fit:** 14/70 (20%) **Discomfort reported:** 39/70 (56%) **Knee length:** **Wearing:** 19/46 (41%) **Appropriate fit:** 12/46 (26%) **Discomfort reported:** 15/46 (33%)	**Funding:** Not stated **Limitations:** ▪ No indication on how timing of checks were determined ▪ Some discrepancies in total number of patients using TEDs and SCDs in the paper. **Additional outcomes:** **Notes:** [#] Discrepancy in total number of patients using/not using SCDs- total 137 for % of patients reported types of SCDs used vs 131 for total of patients using vs not using SCDs

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	<u>All patients</u> **N:** 137 out of 150 approached agreed to participate **Drop outs:** 5/137 ("feeling tired") **Male/Female:** 65/72 **Age ,** years, range **:** 18 to 92 **% of patients observed to be in bed at time of survey:** 117/137 (85.4%)	The survey content validity established with clinical nurse experts and piloted with the data collectors for clarity and revisions were made by consensus of nurse experts. Inter-rater reliability established (93%) between the 6 data-collectors.	**Observation of TEDs usage at time of survey**	**<u>Overall:</u>** **Wearing:** 86/137 (62.8%) **Not wearing:** 51/137 (37%) **Appropriate fit:** 35/86(41%) **<u>Thigh length</u>**[##]**<u>:</u>** **Wearing:** 58/74 (78%) **Discomfort reported:** 43/74 (58%) **<u>Knee length</u>** **Wearing:** 28/41(68%) **Discomfort reported:** 5/41 (12%)	[##] Discrepancy in reported in the report – 60% (82/137) reported using thigh length, but number of patients using vs not using totalled up to 74 TEDS= thromboembolic deterrent stockings SCD = sequential compression device. This is also known as intermittent pneumatic compression devices (IPCD)
			Reasons for not using SCD (N=91) (multiple responses allowed: total of 149 responses)	▪ Had a good reason (just had a bath, ambulated): 46% ▪ SCDs were uncomfortable (hot, itchy): 39% ▪ Registered nurse had never initiated them or had not replaced them after transfer from another unit: 13% ▪ Did not know they were off: 2%	
			Reasons for not using TEDS (N=51) (multiple responses	▪ TEDs were uncomfortable (hot, itchy): 43/51(84%, 59% of responses) ▪ Had a good reason (just had a bath, ambulated): 17/51 (33%,	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			allowed: total of 73 responses)	23% of responses) ▪ Registered nurse had never initiated them or had not replaced them after transfer from another unit: 12/51(23.5%, 16% of responses) ▪ Did not know they were off: 1/51(2% of responses)	
			Easy to put on	**SCDS:** 65% **TEDS:** 46% (30% reported difficult to put on and this was not related to length of stockings)	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chan et al., 2007[47] **Study design:** Observational & cross sectional survey **Evidence level:** + **Duration of follow-up:** Short term prophylaxis	**Patient group:** Lower limb arthroplasty. Trauma patients mostly excluded **Setting:** Department of Orthopaedic and Trauma surgery, Merlin Park Regional Hospital, Galway, Ireland. Patients were from 3 wards, recruited over a 5 months. **Inclusion criteria:** "fully evaluated to the satisfaction of the authors". Complete scheduled observation and questionnaire completion. **<u>All patients</u>** **N:**30	AV Impulse System (Orthofix Vascular Novamedix, Andover UK). Patients required to wear them at all times except during mobilisation on the first operative dat. Patients kept on bed rest 24 hours post arthroplasty and generally commence mobilisation on the first postoperative day. **Methods:** 1. Spot checks randomly performed and recorded at least 1 hour apart, up to 3 checks per day, until patients were found to be non-compliant for 2 consecutive days. Checking times randomised using computer generated random number. Patients and nursing staff unaware that checks were recorded to avoid bias. % of compliance of each patient = number of compliant checks/total number of checks *100% 2. Survey – patients completed questionnaire on day of discharge	**Level of compliance (%)** As shown in graph (exact values not provided)	**Day 1:** 100 **Day 2:** 90-100 **Day 3:** 80-90 **Day 4:** 50-60 **Day 5:** 30 **Day 6:** 20 **Day 7:** 10-20 **P value:** <0.001 using chi-square test from day 3 to 5	**Funding:** Foot pump manufacturer: Novamedix, Andover UK **Limitations:** ▪ Selectiveness of patients included in the analysis – stringent requirement may caused bias and limit external generalisability. ▪ No report of questionnaire validation ▪ Patient's awareness and consent of participation in study may bias compliance rates ▪ Number of patients who were eligible but refused to participate/excluded was not reported
			Correlation of compliance with age	**Spearman rank correlation coefficient, r = -**0.495 **P value** < 0.01 (compliance decrease with increasing age)	
			Comfort level (measured by visual analogue scale of 1-10)	**Mean :** 7.1 (definition of 7.1 not provided)	
			Perceived purpose of device (question: "why are you wearing foot pumps"?) For circulation		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Type of procedures: 21 THR, 6 TKR and 3 bipolar hemiarthroplasties **Age**, years, mean ± SD: 72.4±11.2 (range 44-91)		Don't know To prevent clot Help with mobility/walking To reduce leg swelling To support/splint the leg	14/30 (46.7%) 8/30(26.7%) 4/30(13.3%) 3/30(10.0%) 2/30(6.7%) 1/30(3.3%)	**Additional outcomes:** **Notes:** Same foot pump as Pitto2008 and Anand2005
			Factors which discourage patients from wearing foot pumps: Sleep patterns disturbed Feet feel too hot Disturb other patients in the ward Too much pressure Noise disturbance/alarm Pump activated too frequently	17/30 (56.7%) 13/30 (43.3%) 11/30 (36.7%) 9/30 (30.0%) 8/30 (26.7%) 5/30 (16.7%)	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Haddad et al., 2001[133] **Study design:** RCT **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Elective hip surgery-primary or revision **Setting:** Vancouver , Division of Reconstructive Orthopaedics in a large teaching hospital **Inclusion criteria:** Patients prospectively at random from 1 of 4 orthopaedic surgeons with a major interest in lower limb arthroplasty **<u>All patients</u>** **Before education initiative** **N: 30** **After education initiative** **N: 49**	**IPCD –thigh length, bilateral** Usage followed standard departmental protocol; ▪ All patients should receive pharmacologic and IPCD for DVT and PE prevention. No GCS used ▪ IPCD should be initiated as soon as possible after surgery, ideally within 1 hour post-anaesthetic in recovery room ▪ Interruption allowed when patients were ambulant or undergoing specific treatment such as physiotherapy, change of dressings or investigations. ▪ Any single interruption expected to be , 2 hours and total time should not be >10% in the early postoperative period and not >20% at later periods. Patients should receive ≥21hours/day in the first 2 days and ≥19hours/day subsequently **Method:** ▪ Compliance was measure before and after the nursing education initiative recording using monitoring devices hidden at the bed of study patients for the first 120 hours of use	**Compliance,** % of time using the device, from start to end of study	**Before:** 78±17% **After:** 80.6±14.0%	**Funding:** John Charnley Trust and the BOA/Wishbone Trusts and Norman Capener Travelling Fellowships **Limitations:** Directness of evidence- Canadian study conducted in before mid 1999 **Additional outcomes:** **Notes:** Nursing education was provided: Institutional and manufacturer based on the wards and post-anaesthetic recovery rooms. This comprised supplementary training
			Duration of average interruption, hour, mean±SD, range	**Before:** 3.6±3.0 (0.0 to 15.9) **After:** 2.6±2.7 (0.4 to 12.8)	
			Duration of longest interruption, hour, mean±SD, range	**Before:** 9.3±8.6 (0.0 to 39.6) **After:** 101.+-11.6 (0.7 to 40.0)	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
May et al., 2006[218] **Study design:** Qualitative (interview) **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Mixed medical and surgical patients **Setting:** East Kent, UK **Inclusion criteria:** Patients who had been hospitalised in the past 2 months, and had worn stockings for ≥ 48 hours **All patients** **N:** 12, identified from a convenience sample of 100 patients 9 wore thigh length, 3 wore knee length stockings.	Graduated compression stockings. **Aim of study:** "to explore patient experiences of GCS, to ascertain their perception about their use and care and to identify any limitations in the information currently provided to inform the design of a patient information leaflet" **Methods:** Recruitment: Researchers gave patients who were interested a brief verbal introduction, consent forms and paid return envelopes. Written project information was sent to potential participants, written and verbal consents obtained. Data collection: Telephone interviews were taped and transcribed. Semi-structured interview schedule with open ended questions which had been piloted in 2 subjects were used. Data analysis: Transcripts were verified by participants. Each researcher (8 of them) individually analysed transcripts for emerging themes and consensus was obtained through discussion. Theme saturation was obtained in a sample of 12 patients	**Amount and type of information received:** Most patients (8 out of 12) could not remember receiving information regarding everyday care of compression stockings. **Amount and type of information desired:** ▪ Some patients perceived that nursed would have supplied necessary information. One participant thought that that in a hospital, "you do as you are told". ▪ Some did not think that information is required ("common sense"), while others thought that it is nice to have a leaflet to read and it would have been helpful to have some information in the hospital. **Other sources of information** Most patients had little alternative source of information other than that acquired in the hospital. The other sources were: ▪ Health information from long haul flights ▪ Previous experience with VTE – self or family. **Reasons for wearing compression stockings:** ▪ Not all patients understood the reason to wear GCS. Some understood that it was meant to prevent DVT, but could not relate to their situation since they did not have DVT. ▪ Some patients who did not understand fully thought that		**Funding:** Not stated **Limitations:** ▪ Qualitative study to explore patient experience; not able to tell which concerns were those experienced by most patients **Additional outcomes:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		<u>List of interview questions:</u> ▪ Have you worn compression stockings before? ▪ Hong long did you have to wear your stockings? ▪ How many pairs were you given and what type? ▪ Were you given a new pair? ▪ What was the reason you had to wear them? ▪ How did nursing staff prepare you for wearing stockings? o Were you measured? o Were you given information sheet? o Where you told about laundering, skin care, when to remove stockings, exercise? ▪ Did you experience any problems with your stockings? o Could you put them on/take them off yourself? o Were they comfortable? o Did they fit? o They you wear them for as long as recommended? ▪ What advice would you give to other patients with compression stockings? ▪ Is there anything else you could like to add?	GCS were "given to you for a reason", but it can be taken off if you can't wear them after trying them on. **Experiences with GCS fitting and use** ▪ Poorly fitted stockings – 7 out of 12 were not aware of measured and 2 patients were certain they had not been measured. ▪ There was a lack of information about how to put on and take off the stockings, or how it should fit. Some patients obtained the information from other patients, family and friends or other health care professionals, and this resulted in a variety method which may not be appropriate. ▪ Practical problem of putting on and taking off the stockings. Although help from nurses was received initially, this did not always continue. ▪ Latex allergy – blisters form at the top of the stocking. Patient was subsequently given instructions which would have caused wrong fitting (turn the top back slightly). ▪ Confusing or lack of information on duration of putting on the stocking, when to take them off/change them off, particularly whether to stop wearing them or continue wearing them at home. ▪ Most patients did not receive information about how to take stockings off and wash them, resulting them relying on "common sense "and used inappropriate methods. ▪ Lack of information given about prophylactic exercises. ▪ Varied comments about appearance and comforts. Patients found that the stockings were more comfortable that they had imagined.		

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Murakami et al., 2003[233] **Study design:** RCT **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** trauma patients **Setting:** From emergency department until discharge **Inclusion criteria:** ▪ Projected hospitalisation of ≥12 hours ▪ Able to have IPCDs applied to both legs ▪ ≥18 years ▪ No history of venous thromboembolism or requirement of systemic anticoagulation **All patients** **N:** 33 Revised trauma score: 11.7 **Group 1:** SCD-calf length, N=16 **Group 2:** CECT, =17 **Type of injury: SCD/CECT** ▪ Head: 3/3 ▪ Spinal cord:1/1 ▪ Pelvic :4/1	**Group 1:** SCD-calf length **Group 2:** CECT **For all patients:** ▪ Compression begin immediately after randomisation; study end upon patient discharge ▪ Nursing staff and physicians taught how to use devices ▪ Investigators made no attempt to influence the use of devices once patients enrolled into the study. **Compliance measurement:** counters affixed to the devices to measure the amount of time the device was applied and pumping, and this was checked twice daily to ensure they were working	**Compliance** (total number of minutes device was pumping/ total number of minutes patient was enrolled) * 100%, mean±SD (n)	Emergency department **Group 1:** 57.8±10.5 (12) **Group 2:** 100.0±0.0 (11) **P value:** 0.002* Operating room **Group 1:** 22.1±22.1(4) **Group 2:** 57.1±20.2(7) **P value:** 0.28* ICU **Group 1:** 69.9±12.5(8) **Group 2:** 70.1±10.8(12) **P value:** 0.99* Nursing ward **Group 1:** 46.0±7.2(16) **Group 2:** 72.8±6.1(17) **P value:** 0.008† Total **Group 1:** 58.9±4.6 (16) **Group 2:** 77.7±3.9 (17)	**Funding:** Not stated **Limitations:** ▪ Small sample size ▪ Paper stated no attempt was made by investigators to influence pump use after enrolment. However, awareness of RCT participation could have affected the patients and nursing staff **Additional outcomes:** Venous flow velocities of the two devices **Notes:** SCD – sequential compression device, also known as IPCD (intermittent pneumatic compression device) CECT = continuous enhanced

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	▪ Lower extremity:1/5 ▪ Chest:1/3 ▪ Abdominal:3/1 ▪ Others:3/3			**P value:** 0.004† * calculated by authors using Mann Whitney U test † calculated by authors using independent student t-test	circulation therapy group. This is a miniaturised and portable IPCD which is battery powered.

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pagella et al., 2007[247] **Study design:** RCT & cross sectional survey **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Orthopaedic trauma with surgical procedure of THR/THR patients **Setting:** Transitional trauma and orthopaedic medical –surgical unit, Pennsylvania US, in Feb2002 to July 2002 **Inclusion criteria:** Age> 18 years, physician ordered IPCD **All patients** **N:** 70 (74 patients approached) **Dropouts:** 5 (1 unreliable historian, 2 lost to follow up, 2 with missing data)	IPCD, calf length. Patients randomised to two devices with different sleeve materials 1) Thick stiff plastic 2) Breathable **Methods:** Patients were randomised for either type of device. Nursing staff continued to encourage patients to use the pumps for the maximum number of house possible per day Standardised informational handouts were provided to both groups. On day 3 or at discharge, the patients were given the questionnaire to assess comfort, satisfaction and compliance. Nursing staff complete questionnaire on their	**Patient questions:** (5=strongly agree, 4=agree, 3=neutral, 2=disagree, 1=strongly disagree) Comfortable Interfered with movement Kept patient awake Loud Hot Made leg sweat Used in bed Used on chair Would not use again **Adherence** (% time device was used in 24 hours)	**Thick plastic vs breathable material** 4.3 vs 4.4 2.1 vs 1.3 1.7 vs 2.0 1.5 vs 1.5 2.2 vs 1.5 2.6 vs 2.0 4.7 vs 4.8 2.0 vs 2.3 2.1 vs 2.4 **Patient reported:** 81-85%, N=58 **Nursing staff reported:** 66-71%, N=22	**Funding:** Not stated **Limitations:** Compliance rate generalisability limitation because: ▪ Data obtained from a RCT setting, therefore compliance rate likely to be higher ▪ Patient self reported compliance – potential bias to be higher ▪ Nursing staff rating of their impression of compliance for all patients cared at the end of study ▪ No objective methods of compliance measurement

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		impression of the devices at end of study			**Additional outcomes:** IPCD = intermittent pneumatic compression device

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Parnaby, 2004[255] **Study design:** Observational **Evidence level:** + **Duration of follow-up:** Cross sectional- one day	**Patient group:** Inpatients **Setting:** 16 mixed surgical specialty wards in Middlesex Hospital, London. January 2003 **Inclusion criteria:** All patients **All patients** **N:** 218	Hospital has an written policy that all patients should be wearing anti-DVT stockings, unless it is contraindicated (peripheral vascular disease or profound limb ulcerations) **Methods:** Each patient was asked and checked to see whether they were wearing GCS-length was noted (thigh vs knee)	**Number of patients wearing observed to be wearing GCS, and wearing it correctly**	**Wearing any GCS:** 99/218 (45%) **Wearing any GCS correctly:** 87/218 (40%) Breakdown by stocking length **Wearing above knee product:** 13 (6%) **Wearing above knee product correctly:** 9/13 (69%) ["Approximately one third wear incorrectly"- rolled or folded down the knee] **Wearing below knee product:** 86 (46%) **Wearing below knee product correctly:** 78/86(91%)	**Funding:** Not stated. **Limitations:** Study conducted **Additional outcomes:** Outcomes (comfort, quality, instruction, and ease of use) from two related trials of UCL developed GCS was also reported. **Notes:** Survey was conducted before the initiation of two trials of GCS products developed by UCL (University College London)

Patient views on mechanical prophylaxis

Study details	Patients	Intervention/Methods	Outcome measures	Effect size	Comments
Pitto & young, 2008[261] and Pitto & young, 2008[260] **Study design:** Observational & cross sectional survey **Evidence level:** + **Duration of follow-up:** Short term prophylaxis	**Patient group:** Total joint replacement (hip or knee), degenerative osteoarthritis **Setting:** Department of Orthopaedic surgery, Auckland **Inclusion criteria:** Consecutive patients admitted from Jan 2003 to Dec2005 **Exclusion criteria:** Patients with diabetes, active malignant tumour, gastrointestinal ulcer, bleeding diathesis and superficial wounds or painful joints **All patients** **N:** 846	**Group 1:** Foot pump + 100mg aspirin (3 orthopaedic surgeons, 1 did not use aspirin) **Group 2:** Foot pump + GCS +100mg aspirin (3 orthopaedic surgeons) GCS used were either thigh or knee length Foot pump used ; AV Impulse System (Orthofix Vascular Novamedix, Andover UK) Foot pump usage: Nurses told to activate foot pump when patients were not weight bearing. Foot pump set at 20/1, with pressure of 130mmHg applied for 1s. Compliance measurement: by internal meter which measured the number of hours the foot pumps of switched on. Patients considered as discontinued foot pump when foot pump not used for 4 continuous hours.	**Discontinued foot pump** (between days 2 and 6, mean 3.2 days.) **Reason for termination:** **Discomfort (around the ankles)** **Sleep disturbances** **Patient opinion about foot pump:** **Painful** **Annoying/difficulty with sleeping** **Uncomfortable** **No discomfort**	Total: 46/846 (5.4%) **Group1:**10/416 **Group2:**30/436 **RR:** 0.55 (95% CI:0.31 to 0.99) **P value:**0.049# 14/46(0.3%) 32/46(69.6%) 3/800 (0.4%) 70/800 (8.8%) 10/800 (12.5%)	**Funding:** Not stated Manufacturer: Novamedix, Andover UK **Limitations:** ▪ Method of eliciting opinion about comfort of foot pump not described ▪ Discrepancy in number of denominator 846 vs 800 [author confirmed 46 dropped out, but did not explain the discrepancy in denominator values] **Additional outcomes:** ▪ Number of DVT events and side effects such as bleeding

Study details	Patients	Intervention/Methods	Outcome measures	Effect size	Comments
			Relaxing	505/800 (63.1%) 212/800 (26.5%)	**Notes:** Same foot pump as Anand2007 and Chan2007A #Calculated by NCC-AC team
			Number of hour used per day (mean, range)	15.9 (14-20.5)	

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Robertson et al., 2000[275]	Comparative study	2	**Total**: 224 **Intervention:** n = 120 **Control:** n = 104	**Type of surgery:** Hip replacement	**Type**: Foot pumps (Plexiplus) **Duration**: started on day of surgery and continued until postoperative day 3 Warfarin or heparin was also given to some patients at the discretion of the surgeon **Additional non-comparative prophylaxis:** Not reported	**Type**: Thigh high sequential compression devices (**SCD**) (Kendall) + graduated compression stockings **Duration**: 4 postoperative days Warfarin or heparin was also given to some patients at the discretion of the surgeon **Additional non-comparative prophylaxis:** Not reported	4 days	Average no. of hours per day devices worn	Average number of hours worn per day from the day after surgery: **Int:** 17.4 **Control:** 18.1 **P value:** Not sig Number of hours worn on surgery day: **Int :**8.8 **Control:** 9.8 **P value:** Not sig	
								No. of patients responding as 'comfortable' or no complaints with intervention	**Int:** 85/120 **Control:** 57/104 **p value:** 0.037	
								Reasons for non-compliance with foot pumps	Painful to foot/heal: 5/120 Forceful pulsation: 4/120 Tight: 3/120 Blisters: 1/120	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								Reasons for non-compliance with sequential compression	Hot/sweaty: 14/104 Stockings bothersome: 9/104 Tight: 4/104 Itchy: 4/104 Blisters: 2/104	
								Preference for device in foot pump patients having revision surgery who had previously received SCD.	Foot pump: 24/35 (68.6%) SCD: 7/35 (20%) **p value:** <0.005 No preference: 4/35 (11.4%)	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Stewart et a., 2006[305] **Study:** Observational **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Surgical patients **Setting:** Santa Barbara, California in a single community teaching hospital **Inclusion criteria:** All patients admitted to the surgical service who had IPCD ordered **All patients** **N:** not reported	**IPCDs** – all patients received **Nurse education** : "Group discussion with nurses", to provide information on benefits and purpose of wearing IPCDs, followed by a question and answer **Patient education:** handing out a one page flier with this statement: "Please notify your nurse if your compression stockings are not on. They are important for preventing blood clots during the hospital stay" **Method:** Residents documented compliance, ie patients had pneumatic stockings attached to both legs and to the pump, and pump was activated. This data was collected twice daily (morning and evening) for a period of two months. Data on morning and afternoon rounds was counted as separate patient entries to evaluate the different nursing shifts taking care of patients	Compliance, observed twice daily based on number of observations.	Before education initiative Surgical ward: 131/213 (61.5%) Non surgical ward: 73/152 (48%) After education initiative Surgical ward: 93/142 (65%) Non-surgical ward: 73/152 (48%)	**Funding:** **Limitations:** Sample size unknown, since outcome reported based on number of observations **Additional outcomes:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		None of the nurses or patients were aware of the study			

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Van Blerk et al., 2004[323]	Case series	3	**Total**: 30 **Mean (range) age:** 68 (23-97) **M/F:** 10/20	**Type of surgery:** Elective joint replacement on 2 wards 27 of the patients described as having major orthopaedic surgery **Excluded patient groups:** suspected of having VTE severe peripheral arterial disease severe heart failure any local condition in which garments may interfere such as infections, recent skin grafts or dermatitis	**Type**: IPCD device Flowtron ® Universal DVT Prophylaxis System, Huntleigh Healthcare Ltd Calf garment: n=19 Foot garment: n=10 Calf & foot: n=1 Garment size determined by size of patient, size of limb and surgical procedure **Duration**: mean duration 7 days **Additional non-comparative prophylaxis:** A range of prophylactic procedures being used, around 25% patients used IPCD	Not applicable	7 days	No of patients describing the system as comfortable or very comfortable No. of nurses described as rating the device "highly positively"	23/27 20/20	Reported no patients received VTE during study period but not stated whether patients were screened **Funding** Not reported

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
					alone					

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Westrich et al., 2003[335]	Prospective case series	3	**Total**: 100	**Type of surgery:** Knee arthroplasty	**Type:** Pulsatile pneumatic plantar compression PlexiPluse foot wrap Observation started postoperatively and continued until device no longer used. **Additional non-comparative prophylaxis:** Not reported	not applicable	1 hour	**Total 'compliance' recorded by observer** (total time of observed use / total time observed)	Nurses: 5537/6356 hours (87.1%) Researchers: 1314/1970 hours (66.7%) Combined nurses and researchers: 6851/8426 hours (81.3%)	For time used there are two lots of results assessed: nurses assessed use for 24 hours per day, research team assessed use between 9am and 5pm. *Actual compliance excluded times when the device had to be removed such as going to physiotherapy, ambulatory activities, hygiene and for tests conducted in another room.
								Actual 'compliance' recorded by observer (total time of observed use / total time observed that a patient can use the device)*	Nurses: 5537/5957 hours (92.9%) Researchers: 1314/1646 hours (79.8%) Combined nurses and researchers: 6851/7603 hours (90.1%)	

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Wood et al., 1997 [343]	RCT	1+	**Total**: 134 **Intervention:** n = 75 **Control:** n = 59	**Type of surgery:** Anterior lumbar interbody fusion, posterior spine fusion, posterior lumbar interbody fusion, **Intervention**: Mean age: 39.4 (sd 17.2) yrs M/F: 39/36 **Control**: Mean age: 39.6 (sd 18.5) yrs M/F: 39/20	Patients wore thigh-high compression stockings + Foot wraps **Additional non-comparative prophylaxis:** Not reported	Patients wore thigh-high compression stockings + Sequential Pneumatic Compression Wrap	Scanning carried out between post-operative days 5 and 7	**DVT** Confirmed by: Duplex US	**Int:** 1 **Control:** 0 **p value:** N/A	**Comments:** 36 patients (26%) complained of redness, itching, or actual discomfort with the use of the devices. No symptomatic DVTs of PEs **Not reported:** Survival, PTS, bleeding related complications, QoL and LoS
								PE Confirmed by: Duplex US	**Int:** 1 **Control:** 0 **p value:** N/A	
								Visual analogue comfort scale (mean ±SD)	**Int:** 5.84 ±2.8 **Cont:** 5.56 ±2.9 **p value:** 0.88	

Patient views on heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chiou-Tan et al., 2003[50] **Study design:** RCT, cross sectional observation and survey **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Spinal cord injury **Setting:** Multiple hospitals in Houston, Texas. **Inclusion criteria:** Sequential patients with acute, complete or incomplete spinal cord injury, within 3 months of date of injury. **All patients** **N:** 100 patients were recruited, and 95 met all inclusion criteria. 80 patients completed questionnaires upon study completion. **Age:** 16-65	**Group 1:** enoxaparin 30 mg, administered subcutaneously 12 hourly **Group 2:** dalteparin, administered once a day During hospitalisation the LMWH was administered by nursing staff. At discharge, the patient or family members received instructions on how to administer injections at home. They received a call every two weeks from research assistant to remind them to fill up log book and determine if there were any problems in getting refills. **Methods:** Log books to collect compliance data Questionnaires at follow up to determine pain, compliance and difficulties related to injections. Scale of 1 to 10.	**Compliance rates** (as recorded in log book of administration time)	Hospital logs **Group 1:** 99.2% **Group2 :** 99.5%	**Funding:** Not stated **Limitations:** ▪ No mention of questionnaire validation ▪ For questions regarding hassles, patients answered that to the hypothetical scenario of taking tablets 3 times per day ▪ Questionnaire format and answer options not provided **Additional outcomes:** The same outcomes – compliance, pain rating and hassles were also obtained from patients who received injections at home.
			Painfulness of injections, mean ± sd, (range) 1=not painful at all, 10=extremely painful	Patients in hospital **Group 1:** 1.45±0.96 (1-4), n=22 **Group2 :** 1.63±0.83 (1-3), n=19 **All:** 1.53±0.61 (1-4)	
			Frequency of missed injections, mean ± sd, (range) 1=never missed, 10=very frequently missed	Patients in hospital **Group 1:** 1.05±0.24(1-2), n=22 **Group2 :** 1.11±0.32(1-2), n=19 **All:** 1.08±0.16, (1-2)	
			Hassle of injections compared to taking pills 3 times a day, mean ± sd, (range) 1= much less of a hassle, 10=very much more of a hassle)	Patients in hospital **Group 1:** 2.82±3(1-10), n=22 **Group2 :** 2.16±1.98(1-7), n=19 **All:** 2.51±2.16, (1-10)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Male/female: 72/23 Most patients were recruited within 4 weeks of injury				

Patient views on heparin

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Colwell et al., 2005[67]	Case series	3	**Total**: 61 11 excluded Discharged to nursing facility: 5 Surgery cancelled: 2 Using anticoagulant: 1 Retinal hemorrhage before surgery: 1 Withdrew consent: 2	**Type of surgery:** Primary or revision elective total hip and knee surgery. **Age**: 40 to 70 years	**Type**: Self injection of low molecular weight heparin (Enoxaparin) **Dose:** 30mg per day at 9am and 9pm for postoperative days 1 to 7 40mg per day at 9am for postoperative days 8 to 21 Staff nurses gave first injections and explained purpose of heparin, discussed patient's responsibilities following discharge. Patients (or family member) demonstrated their technique. Patients also given a take home self injection kit that included and instructional video developed by the manufacturer and written instructional materials outlining	**not applicable**	21 days postoperatively	**Concordance with self injection**	22/40 fully coconcordant:(all doses within one hour of scheduled time) 15/40 partially coconcordant: (at least 6 days of 30mg every 12 hours then at least 13 days of 40mg once per day. All doses within 2 hours of scheduled time) 3/40 non concordant	**Comments:** **Funding**: not reported but manufacturers supplied a video for each participant on injection technique. **Also reported:** No. of patients understanding the importance of self injection No. of patient comfortable giving injection Mild burning and stinging at injection site Mild bruising at injection site

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
					injection technique and potential side effects.					**Not reported:**

Patient views on heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Noble et al., 2006[240] **Study design:** Qualitative (interviews) **Evidence level:** + **Duration of follow-up:** Long term	**Patient group:** Metastatic cancer or primary brain tumour with no curative treatment available **Setting:** Specialist palliative care unit within the regional cancer centre (Cardiff), which had established thromboprophylaxis guidelines. **Inclusion criteria:** ▪ Evidence within medical notes that the incurable nature of the disease has been discussed with the patient ▪ The patient had received LMWH prophylaxis for at	**Aims of study:** "To find out what inpatients with advanced cancer who are receiving palliative care think about the effect of thromboprophylaxis on overall quality of life" **Methods:** Patients identified using screening notes and drug charts. <u>Data collection</u> Semistructured interviews were audio taped and then transcribed. <u>Topics covered:</u> cancer treatments received (such as surgery, chemotherapy, and radiotherapy); insight into prognosis; what was understood about treatment with low	4 major themes and 3 minor themes identified **Knowledge and understanding** ▪ All patients understood the purpose of heparin and many understood why they were at risk; immobility and surgery were identified as risk factors. ▪ All patients knew death is a consequence, but unaware of DVT symptoms such as painful swollen legs, or of pulmonary embolism, such as dyspnoea. ▪ Most knowledge was based on media coverage: Its association with long haul flights, but there were little understanding of the specific association with cancer. **Acceptability** All patients found thromboprophylaxis with LMWH acceptable, and many could not understand why it would be considered unacceptable. Aspects of acceptability ▪ Recognition that thromboprophylaxis with heparin was part of usual practice: They associate it a reassurance that something is being done for them, and getting the best care. ▪ They considered treatment with heparin was neither pleasant nor unpleasant ▪ Balance of benefits against side effects		**Funding:** Velindre small grants scheme **Limitations:** ▪ Qualitative study – range of opinions elicited by % of patients with these views not known ▪ Questions and probes used not reported ▪ Aim stated as effect on overall quality of life but results focused more on acceptability **Additional outcomes:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	least 5 consecutive days **<u>All patients</u>** **N (all):** 28 **<u>Patients admitted after spinal cord compression</u>** N=14 **Age** (range): 55-74 **M/F:** 7/7 **Type of cancer:** breast: 5; prostate 3; lung: 2; unknown:2; ovarian: 1; colon: 1 **Treatment:** chemotherapy and radiotherapy 5; surgery, chemotherapy, and radiotherapy 4; radiotherapy 2; surgery and radiotherapy 2; surgery and chemotherapy 1 **Preadmission ECOG scores :** 0-2 **Previous thromboprophylaxis:** none 8; LWMH: 1; LMWH + GCS: 3; GCS: 3 **<u>Patients admitted primarily for symptom control</u>**	molecular weight heparin and thromboprophylaxis; the impact of thromboprophylaxis on overall quality of life; negative aspects of being on heparin treatment. <u>Analytical framework and data analysis:</u> Thematic analysis, using an inductive approach. Patients recruited until theoretical saturation (when no further recurring themes emerged from analysis) was achieved.	**Reassurance and optimism** ▪ Patients understood that they had a terminal illness but expressed a desire to optimise quality of life not only by treating symptoms but also by taking measures to prevent other symptoms. ▪ Thromboprophylaxis with heparin reassured most patients that something was being done to prevent other problems and that the medical team had not given up on them. **Views and concerns about thromboprophylaxis methods and side effects** ▪ <u>Bruising</u>: Bruising was the only negative experiences reported from LMWH but that did not seem to be a big concern/bother, especially when compared with the treatments and side effects experienced for cancer. ▪ <u>Discomfort from GCS:</u> Several patients had worn GCS during previous hospital admissions and all had found them uncomfortable (hot, itchy and tight), and not acceptable for long term wear. LMWH would be preferable **Terminally ill patients wish to be involved in decision making about thromboprophylaxis** ▪ Patients uniformly expressed their need to be involved in decision making, particularly with respect to the withdrawal or non-administration of treatment. Some patients had experienced what they viewed as nihilistic paternalism, and they were angry that major decisions were made about their lives without their involvement.		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (range): 53-76 **M/F** : 5/9 **Diagnoses:** pancreatic: 3; ovarian: 2; colon: 3; breast: 2; lung: 1; unknown 1; brain: 1, uterine: 1 **Treatment:** none 1; chemotherapy and radiotherapy 1; surgery and radiotherapy 2; surgery and chemotherapy 2; chemotherapy 2; surgery, chemotherapy, and radiotherapy 3; radiotherapy 3 **Preadmission ECOG scores:** 1-3 **Previous thromboprophylaxis:** none 9; LMWH: 2; GCS: 2; LMWH + GCS: 1				

Patient views on heparin

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Spahn et al., 2002 [300]	Case series	3	**Total:** 207 **Age:** <20 yrs: 26 20-40 yrs: 82 40-60 yrs: 51 >60 yrs: 48 300 patients included in the study, 220 returned the questionnaire, 13 were incomplete.	**Type of surgery:** Knee arthroplasty	**Type:** Injection of low molecular weight heparin (Fraxiparin) Injection by: Self: n = 160 Family member or friends: n = 31 Nursing service: 16 **Dose:** Depended on body weight and further risk factors. Instructions were given by a physician or qualified nurse. Patients carried out first and last injection in the presence of the instructor and got a pack containing 10 syringes, disinfection swabs and an information brochure.	**not applicable**	10 days post-operatively	**Problems with self /family member injection**	None: 107/191 (56%) Initially: 72/191 (37.7%) All the time: 12/191 (6.3%)	**Comments:** Not reported **Funding:** Not reported **Also reported:** **Not reported:** Not reported
								Perception of injection 'very unpleasant'	Injection by: Self: 18/160 (11%) Family: 9/31 (29%) Nurses: 5/16 (31%)	
								No. self/family member infection patients with unsure prophylaxis	54/191 (28.3%)	
								No. self/family member infection patients who forgot prophylaxis	34/191 (17.8%)	
								No. self/family member infection patients discontinued injections early	25/191 (13.1%)	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
					Assessment of patient use by anonymous questionnaire.					

Patient views on pharmacological and mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Anand & Asumu, 2007 [6] **Study design:** Cross sectional survey **Evidence level:** + **Duration of follow-up:** Short term prophylaxis	**Patient group:** Hip and knee replacement, **Setting:** Royal Oldham Hospital, Oldham, UK **Inclusion criteria:** Consecutive elective THR or TKR patients who were able to give informed consent **Exclusion criteria:** Gastrointestinal ulceration or painful foot conditions **<u>All patients</u>** **N:** 43 **Male/Female:** 14/29 **Age, mean:** 69.9 (range 36 t o 85) **Type of surgery:**	**All patient received:** 1. LMWH (dalteparin): once daily, subcutaneously through abdominal wall using 26 gauge needle, starting 12 hours before surgery and 24 hours thereafter 2. Foot pumps (A-V Impulse System, Novamedix, Andover UK): applied to both feet, in the recovery room after operation, and used whenever patient not weight bearing. Pump activated every 20s to a pressure of 130mmHg for a period of 1s. **Methods:** Patients asked to inform nurses if they find any of the methods uncomfortable and wished to discontinue Patients surveyed on day of discharge with questionnaires which consistent of a visual analogue scale (VAS) to mark level of comfort associated with thromboprophylaxis method and agreement to statements (choice of "strongly disagree", "disagree", "neutral", "agree", "strongly agree")	**Comfort** VAS scale score, 0= most uncomfortable, 10= most comfortable **Painful:** "agree" or "agree strongly" **"rather not have these"**, "agree" or "agree strongly" **" willing to continue these ... at home for 4 weeks after my discharge from the hospital"** : "agree" or "agree strongly" **Discontinuation of foot pump in hospital due to pain** (one in day 2, the other in day 3) The foot pumps: ▪ comfortable ▪ restrict mobility ▪ soothing effect ▪ interfere with sleep	**LMWH:** 6.3 **Foot pumps:**7.3 **P value (t-test):** 0.07 **LMWH:** 5/43 (11.6%) **Foot pumps:** 6/43 (14.0%) **LMWH:** 6/43 (14.0%) **Foot pumps:** 16/43 (37.2%) **LMWH:** 33/43 (76.7%) **Foot pumps:** 22/43 (51.2%) 2/43 (4.7%) 22/43 (51.2%) 28/43 (65.1%) 23/43 (53.5%)	**Funding:** Not reported. Foot pump manufactured by Novamedix, Andover UK **Limitations:** ▪ Validation of questionnaire not reported ▪ Errors in some of the percentages reported; inclusion of neutral answers to the % of patients who would rather not have injections or foot pumps **Additional outcomes:** <u>For foot pumps only</u> : comfort, restriction of mobility, soothing effect, interference with sleep, preferred time of use, willingness to us again if have another operation

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	▪ **TKR:** 27/43 (one with bilateral knee replacements) ▪ **THR**: 16/43 **Length of hospital stay:** mean of 6.58 days (mode of 7 days)		Preference for usage: ▪ only during day time ▪ only at night ▪ during the day and the night ▪ If I have another hip or knee operation, I would like to use the foot pumps	12/43 (27.9%) 19/43 (44.2%) 16/43 (37.2%) 12/43 (27.9%) 31/43 (72.1%)	**Notes:** Same foot pump as Pitto2008 and Chan2007A

Patient views on mechanical vs pharmacological

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Maxwell et al., 2001 [217]	Questionnaire of views and concordance carried on participants of RCT	3	**Total:** 228 **Intervention:** n = 104 **Control:** n = 103 Not all patients in trial were lost to follow up or incapable of participating in postoperative survey.	**Type of surgery:** "Major" procedure for gynaecological malignancy **Intervention:** Median age: 62 (35-85) yrs Gender not reported Mean duration of surgery: not reported **Control:** Median age: 60 (41-87) years Gender not reported Mean duration of surgery: not reported	**Type:** External pneumatic compression sleeves **Timing:** Started with induction of anaesthesia and continued for first 5 days postoperatively. Device stopped when patient was walking and restarted when back in bed. **Additional non-comparative prophylaxis:** Not reported	**Type:** Low molecular weight heparin (Dalteparin) **Dose:** 2500 units subcutaneously 1-2 hours before surgery and 2500 units 12 hours after first dose. Then from postoperative day 1 5000 units per day up to post operative day 5. If the patient was confined to bed after day 5, continued prophylaxis until day of discharge or ambulatory. **Additional non-comparative prophylaxis:** Not reported	**Control:** 5 days **Int:** 5 days (patients also telephoned 30 days postoperatively and questioned for signs and symptoms of delayed VTE)	**Overall comfort/pain** **Suboptimal performance or administration of prophylaxis** **Postoperative preference for the intervention used** **Postoperative preference for other intervention**	**Int:** 26% **Cont:** 4% **Int:** 10/104 **Cont:** 6/103 **p value:** not significant **Int:** 74% **Cont:** 78% **Int:** 3 **Cont:** 4%	**Comments:** Screened everyone for DVTs, only reported proximal. Trial designed to detect differences in complications. **Funding:**not reported **Also reported:** No significant difference in proximal DVTs, median external bleeding loss, thrombocytopenia. **Not reported:** All DVTs, PE, postthrombotic leg, QoL, survival, length of hospital stay

H.7 Nursing care: Early mobilisation and hydration

H.7.1 Early mobilisation and leg exercises

No relevant clinical studies were identified.

H.7.2 Hydration

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Janvrin et al., 1980[157]	RCT	1+	Total: 60 Intervention: 30 Control: 30 Dropouts: 3	Type of surgery: Routine abdominal surgery (any patient requiring blood transfusions perioperatively was withdrawn from the trial). Intervention: Mean age: 57±10 yrs M/F:15/15 Control: Mean age: 58.0±12 yrs M/F: 12/18.;	Type: Intravenous Hartmann‟s solution/ Dextose-saline Dose and timing: 1 litre of per hour of operation. 2-3 litres of dextrose saline 24hs for 2 days. Additional non-comparative prophylaxis: Not reported	Type: No IV fluids during or postoperatively. Water by mouth. Dose: “Small, increasing amounts of water were taken by mouth from the first day onwards”. Timing: Not reported Additional	7 days	DVT measured by FUT. Bilateral daily then alternate days.	Int: 9/30 Cont: 2/30 p value: <0.03	Comments: Three dropouts, but analysis by denominators of 30, i.e. presumably analysed by intention to treat. Also measured risk factors (varicose veins, smoker, etc), impendance clotting time and packed cell volume. Not reported: PE, PTS, QoL,

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
						non-comparative prophylaxis: Not reported				LoS, survival, bleeding, proximal DVT.

H.8 Obesity

No relevant studies were identified.

H.9 People using antiplatelets

No relevant studies were identified

H.10 People using anticoagulation therapy

Study	Di Biase 2014[83]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1584)
Countries and setting	Conducted in USA; Setting: Multi-centre study
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major bleeding was defined as the occurrence of cardiac tamponade or

	hemopericardium requiring intervention, causing symptoms, or requiring transfusion; hematoma requiring intervention; massive hemoptysis; hemothorax; and retroperitoneal bleeding
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with atrial fibrillation undergoing catheter ablation, age ≥18 years, international normalized ratio (INR) in the range of 2.0 to 3.0 in the last 3 to 4 weeks before ablation, and CHADS2 score ≥ 1
Exclusion criteria	Known bleeding disorders or inherited thrombophilic disorder, oral contraceptives or estrogen replacement therapy, prosthetic heart valves, and contraindications to warfarin therapy.
Recruitment/selection of patients	People presenting with AF at the participating centers between December 2009 and December 2012 were enrolled in the study
Age, gender and ethnicity	Age - Mean (range): 61-62 years. Gender (M:F): 3:1. Ethnicity: Not reported
Further population details	1. Atrial fibrillation: Atrial fibrillation (All people with AF). 2. BMI: Not stated 3. Mechanical heart valves: Not stated. 4. Medical/surgical: Surgical 5. Renal impairment: Not stated
Extra comments	Atrial fibrillation type: paroxysmal 27%, persistent 23%, LSP 50%
Indirectness of population	No indirectness
Interventions	(n=790) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Warfarin was discontinued 2 to 3 days before the ablation, and patients were bridged with low-molecular-weight heparin. Specifically, 1 mg/kg enoxaparin was administered twice daily until the evening before the ablation procedure. A bolus of 15000 IU heparin was given intravenously before the transseptal puncture. A continuous infusion of heparin 1000 U/h was started. The infusion was adjusted to maintain an activated coagulation time (ACT) >350 seconds. During the procedures, the transseptal sheaths were continuously infused with heparinized saline. Every effort was taken to avoid air embolism. Protamine was administered after completion of the ablation procedure to partially reverse the heparin effect. A single 325-mg aspirin was given in the electrophysiology laboratory. Sheaths were pulled when the ACT was <200 seconds. Three hours after ablation, enoxaparin 0.5 mg/kg twice daily was routinely started. It was stopped when the INR was >2. Warfarin was restarted the night of the procedure. Duration 48 hours. Concurrent medication/care: All patients were on warfarin before the procedure to achieve 3 to 4 weeks of therapeutic INRs, and warfarin was monitored every week for the 3 to 4 weeks preceding the ablation. (n=794) Intervention 2: Vitamin K antagonists - Warfarin (all doses). All patients continued uninterrupted warfarin. If on the day of the procedure patients had an INR >3.5, they were excluded. If the INR was between 3 and 3.5, fresh-frozen plasma was administered a few hours before the procedure. Some patients presented on the day of the procedure with

	a subtherapeutic INR and were not excluded. A bolus of 10 000 IU unfractionated heparin in male patients and 8000 IU in female patients was given before the transseptal puncture. During the procedures, the ACT was kept >300 seconds, and the transseptal sheaths were continuously infused with heparinized saline. Every effort was made to avoid air embolism. Protamine was administered after the completed ablation procedure to partially reverse the heparin effect. Sheaths were pulled when the ACT was <200 seconds. Warfarin was administered the night of the procedure as per the patient's scheduled dose. Duration 48 hours. Concurrent medication/care: The INR had to be therapeutic and was monitored every week for the 3 to 4 weeks preceding the ablation.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) (OFF-WARFARIN) versus WARFARIN (ALL DOSES) (ON WARFARIN) Protocol outcome 1: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 48 hours; Group 1: 8/790, Group 2: 3/794; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Embolic stroke at up to 45 days from hospital discharge; Haemorrhagic stroke at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Santamaria 2013[287]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=203)
Countries and setting	Conducted in Spain; Setting: Study conducted in ten hospitals in Spain
Line of therapy	Not applicable
Duration of study	Intervention time: 5-6 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major bleeding according to at least one of the following criteria: clinically overt bleeding associated with a fall in haemoglobin of at least 2 g/dL or requirement for a transfusion of two or more units of blood, fatal bleeding, or any bleeding requiring treatment cessation. Venous thromboembolism was defined as any symptomatic deep-vein thrombosis (DVT) or pulmonary embolism (PE) confirmed by objective methods (i.e. Doppler ultrasound or ascending contrast venography for DVT, high-probability lung scanning, pulmonary angiography, helical computed tomography for non-fatal PE or necropsy in cases of fatal PE)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 18 years or older; taking VKA treatment for at least 3 months, required outpatient surgery, laparoscopy surgery or invasive procedures; and gave their written informed consent were included in the study.
Exclusion criteria	The exclusion criteria were the following: hypersensitivity to heparin or other pig-derived substances, a history of documented or suspected immune-mediated heparin-induced thrombocytopenia (HIT); an active haemorrhage or increased risk of bleeding due to impaired haemostasis or an organ lesion (e.g. an active peptic ulcer, haemorrhagic stroke, cerebral aneurysm or cerebral neoplasm); severe impairment of hepatic and pancreatic function; injuries to or surgery on the central nervous system, eyes and ears within the previous 2 months; disseminated intravascular coagulation attributable to HIT; acute or sub-acute endocarditis; use of antiplatelet drugs such as clopidogrel or aspirin; anti-thrombin, protein S or protein C deficiency; inability for the patient to be adequately followed-up; end-stage disease or a life expectancy of <3 months; and participation in another study within the previous month
Recruitment/selection of patients	Consecutive patients of both sexes who were aged 18 years or older between February 2007 to January 2009
Age, gender and ethnicity	Age - Mean (range): 71-73 years. Gender (M:F): 1.64/1. Ethnicity: Not reported
Further population details	1. Atrial fibrillation: Atrial fibrillation (Bemiparin 65.5%; UFH 57%). 2. BMI: Not obese (BMI under 30 kg/m2) (Bemiparin 28.1 (4.1); UFH 28.3 (4.7)). 3. Mechanical heart valves: Mitral prosthetic valve 6.65%; Aortic prosthetic valve 8.4%). 4. Medical/surgical: Surgical 5. Renal impairment: Not stated
Extra comments	Type of invasive/surgical procedure: colonoscopy/gastroscopy 40.6%, arthroscopy 1.7%, cystoscopy 1.8%, bronchoscopy

	1.8%, ocular surgery 16.5%, biopsy 10.8%, cutaneous surgery 2.3%, pacemaker battery replacement 2.4%, herniorrhaphy 3.3%, others 14.2% Oral anticoagulant used: acenocoumarol 91%, warfarin 9%
Indirectness of population	No indirectness
Interventions	(n=92) Intervention 1: Low molecular weight heparin (not licensed in UK) - Bemiparin (2500 units once daily - 3500 units once daily). Patients were discontinued the oral anticoagulation therapy (OAT) (day -5 or -3 for warfarin or acenocoumarol patients, respectively), they started blinded bridging therapy (on days -4 to -2 before the invasive/surgical procedure) with bemaparin (3500IU/24 hour + matching placebo 12 hour afterwards, subcutaneously). On the day of procedure, the morning dose was omitted, and all patients received only one injection in the evening (3500 IU bemaparin).The patients restarted OAT on day +1. The study medication was continued up to 5-6 days after the procedure. At the end of this period, if the INR was <1.8 or <2.5 in patients with mechanical prosthetic valves, then bemiparin was continued up to a maximum of 2 days. . Duration 5-6 days. Concurrent medication/care: N/A (n=99) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Patients were discontinued the oral anticoagulation therapy (OAT) (day -5 or -3 for warfarin or acenocoumarol patients, respectively), they started blinded bridging therapy (on days -4 to -2 before the invasive/surgical procedure) with UFH (5000IU/12 hour, subcutaneously). On the day of procedure, the morning dose was omitted, and all patients received only one injection in the evening (5000IU UFH).The patients restarted OAT on day +1. The study medication was continued up to 5-6 days after the procedure. At the end of this period, if the INR was <1.8 or <2.5 in patients with mechanical prosthetic valves, then UFH was continued up to a maximum of 2 days. Duration 5-6 days. Concurrent medication/care: N/A
Funding	Study funded by industry (Sponsored by the Institut de Recerca - Hospital de la Santa Creu i Sant Pau (Barcelona, Spain) and was partially supported by grants from La Generalitat de Catalunya, Laboratorios Farmaceuticos Rovi S.A. (Madrid, Spain) and RECAVA.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEMIPARIN (2500 UNITS ONCE DAILY - 3500 UNITS ONCE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 90 days; Group 1: 0/84, Group 2: 0/93; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular,

retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 90 days; Group 1: 0/84, Group 2: 4/93; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: VTE at 7-90 days from hospital discharge - Actual outcome: Documented symptomatic arterial or venous thromboembolism at 90 days; Group 1: 0/84, Group 2: 2/93; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Embolic stroke at up to 45 days from hospital discharge; Haemorrhagic stroke at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

H.11 Acute coronary syndromes

No relevant studies were identified.

H.12 Acute stroke patients

Study	**TAIST trial trial: Bath 2001[16]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=999)
Countries and setting	Conducted in Belgium, Canada, Denmark, Finland, France, Germany, Irish Republic, Netherlands, Norway, Sweden, United Kingdom; Setting: Multi-centre (33 centres) study

Line of therapy	Not applicable
Duration of study	Intervention time: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by venography or ultrasonography PE: confirmed by high-probability ventilation perfusion scan, pulmonary angiography or necropsy and death Major bleeding: defined as clinically overt bleeding associated with one or more transfusion of at least two units of red cells, a fall in haemoglobin of 20g/L (1.24 mmol/L) or more, bleeding leading to permanent cessation of treatment.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a clinical syndrome of a stroke were eligible for the trial if they were aged between 18 and 90 years, could be treated within 48 hours of stroke onset and had given written informed consent.
Exclusion criteria	Patients were excluded if they met one or more of the following criteria; computed tomographic evidence of intracranial haemorrphage, midline shift of more than 5 mm, or a non-stroke diagnosis; coma (including consciousness score on the Scandinavian neurological stroke scale above 53); stroke complicating trauma or a medical or a medical or surgical procedures; stroke or myocardial infarction within the previous 3 months; preceding moderate or severe disability (modified Rankin scale, 3-5); confounding neurological or psychiatric disease; a condition mimicking stroke (e.g. hypoglycaemia, Todd's paresis); a congenital bleeding disorder; clinically significant blood loss within the previous 3 months or a current active peptic ulcer, significant hypertension within 6 hours of enrolment (systolic blood pressure above 220 mmHg or diastolic above 120 mmHg); significant anaemia (haemoglobin less than 80 g/L, 4.96 mm/L), thrombocytopenia (platelet count less than 100 x10*9/L), liver dysfunction (INR >1.5, aminotransferases more than 3 times higher than normal) or renal dysfunction (creatinine more than 3 times higher than normal); clinical endocarditis; allergic asthma; recent history of long-term systemic steroid therapy, recent anticoagulant therapy or need for therapy or thrombolysis; severe concomitant medical conditions; pregnancy
Recruitment/selection of patients	June 1999 to January 2000
Age, gender and ethnicity	Age - Median (range): 74 years. Gender (M:F): 1.22/1. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable 3. Type of stoke: Ischemic (99.5% of partipicants)
Indirectness of population	No indirectness
Interventions	(n=508) Intervention 1: Low molecular weight heparin (licensed in UK) - Tinzaparin (2,500 units once daily – 9,000 units once daily). Tinzaparin, 100IU/kg daily was subcutaneously administered (stated as medium-dose in the study). Each patient received one injection (LMWH) and two tablets daily (aspirin placebo). Duration 10 days or until discharge if earlier. Concurrent medication/care: Leg compression stockings were recommended in all patients who were not fully

	mobile. Indirectness: No indirectness (n=491) Intervention 2: Aspirin. Aspirin, 300mg (150mg x 2) once daily, orally given. Each patient received one injection (placebo) and two tablets daily (aspirin). Duration 10 days or until discharge if earlier. Concurrent medication/care: Leg compression stockings were recommended in all patients who were not fully mobile. Indirectness: No indirectness
Funding	Study funded by industry (Leo Pharmaceutical Products sponsored TAIST, provided all study medication and materials)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TINZAPARIN versus ASPIRIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 90 days; Group 1: 60/507, Group 2: 58/491
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Not eligible; Group 2 Number missing: 0, Reason: n/a

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 15 days; Group 1: 3/507, Group 2: 9/491
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Not eligible; Group 2 Number missing: 0, Reason: n/a

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 15 days; Group 1: 4/507, Group 2: 4/491
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Not eligible; Group 2 Number missing: 0, Reason: n/a

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 15 days; Group 1: 2/507, Group 2: 2/491
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Not eligible; Group 2 Number missing: 0, Reason: n/a

Protocol outcome 5: Health-related quality of life (validated scores only) at up to 90 days from hospital discharge

- Actual outcome: Modified Rankin Scale (score 0-2) at 90 days; Group 1: 188/507, Group 2: 206/491 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Evaluated the percentage of patients with a score between 0-2. Details of the scale are not reported in the study but the scale is a measure of disability, score 0-2 equate to no disability to slight disability (higher score is worse). Rationale for picking this score range is not reported. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Not eligible; Group 2 Number missing: 0, Reason: n/a - Actual outcome: Barthel Index (score 60-100) at 90 days; Group 1: 313/507, Group 2: 320/491 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Evaluated the percentage of patients with a score between 60-100. Details of the scale are not reported in the study but the scale is a measure of activities of daily living (ADL). Higher score is worse. Rationale for picking this score range is not reported. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Not eligible; Group 2 Number missing: 0, Reason: n/a Protocol outcome 6: Heparin-induced thrombocytopenia at up to 90 days from hospital discharge - Actual outcome: Thrombocytopenia at 15 days; Group 1: 2/507, Group 2: 2/491 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Not eligible; Group 2 Number missing: 0, Reason: n/a	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge;

Study	**Dennis 2009: CLOTS1 trial: Clots 2009[59]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2518)
Countries and setting	Conducted in Australia, Italy, United Kingdom; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: Intervention till mobile. F/u around day 30.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed on a screening compression Doppler ultrasound (CDU). PE confirmed by imaging or autopsy, fatal PE confirmed by autopsy
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	Admitted to hospital within seven days of acute stroke and are immobile (cannot mobilise to toilet) and were recruited within three days of admission.
Exclusion criteria	Peripheral vascular disease and where there was neuropathy where clinician felt stockings would cause skin damage. Subarachnoid haemorrhage.
Recruitment/selection of patients	No further details reported
Age, gender and ethnicity	Age - Mean: 76 years. Gender (M:F): 1:1.02. Ethnicity: Not reported
Further population details	1. BMI : Not stated 2. Renal impairment: Not stated 3. Type of stoke: Mixed (Around 9% had haemorrhagic stroke (not reported separately)).
Extra comments	For patients without capacity, proxy consent was sought.
Indirectness of population	No indirectness
Interventions	(n=1256) Intervention 1: Anti-embolism stockings - Above knee. Graduated compression stockings, sized and fitted by trained nurses, worn 24/7. Duration Until mobile or discharged, patient declined or skin damage. Concurrent medication/care: Anti-platelet and anti-coagulant therapy allowed as per usual practice in each centre (n=1262) Intervention 2: No treatment - Usual care. Avoid stockings. Duration Until discharge. Concurrent medication/care: Anti-platelet and anti-coagulant therapy allowed as per usual practice in each centre
Funding	Academic or government funding (Scottish Government and UK MRC. Stockings provided by industry with no influence on trial.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABOVE KNEE versus AVOID STOCKINGS

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Dead by 30 days at 30 days from admission; Group 1: 122/1256, Group 2: 110/1262; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: Any DVT (proximal or distal) on Doppler ultrasound (symptomatic or at screening @ around day 10 and 30) at 30 days from admission; Group 1: 205/1256, Group 2: 224/1262; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy;

echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE confirmed on imaging or autopsy at 30 days from admission; Group 1: 13/1256, Group 2: 20/1262; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: PE on autopsy at 30 days from admission; Group 1: 1/1256, Group 2: 1/1262; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Technical complications of mechanical interventions at up to 90 days from hospital discharge - Actual outcome: Skin breaks/ulcers/blisters/skin necrosis at 30 days from admission; Group 1: 64/1256, Group 2: 16/1262; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Lower limb ischaemia/amputation at 30 days from admission; Group 1: 7/1256, Group 2: 2/1262; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: DVT (symptomatic) - Actual outcome: Symptomatic DVT (proximal or distal) at 30 days from admission; Group 1: 36/1256, Group 2: 43/1262; Protocol outcome 7: DVT (proximal) - Actual outcome: Proximal DVT at 30 days from admission; Group 1: 126/1100, Group 2: 133/1133;	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge;

Study	**Dennis 2010: CLOTS2 trial: Clots (clots in legs or stockings after stroke) trial collaboration 2010[56]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3114)
Countries and setting	Conducted in Multiple countries; Setting: Hospitals with "well-organised" inpatient stroke service and capacity to perform ultrasounds

Study	Dennis 2010: CLOTS2 trial: Clots (clots in legs or stockings after stroke) trial collaboration 2010[56]
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT detected by compression duplex ultrasonography or venography. PE confirmed on computed tomography pulmonary angiography or ventilation-perfusion isotope scanning or autopsy. Skin concerns confirmed by compression duplex ultrasonography.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Suspected stroke up to a week prior to admission, enrolled within three days of admission, newly immobile (unable to mobilise to the toilet)
Exclusion criteria	Subarachnoid haemorrhage and conditions contraindicating stockings (severe peripheral vascular disease or neuropathy)
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (range): 76 (67-83). Gender (M:F): 1540/1574. Ethnicity: NS
Further population details	1. BMI : Not stated 2. Renal impairment: Not stated 3. Type of stoke: Mixed
Indirectness of population	No indirectness
Interventions	(n=1552) Intervention 1: Anti-embolism stockings - Above knee. Applied by trained nurses. To be worn 24/7 until discharge, unless skin breaks. Duration Up to 30 days. Concurrent medication/care: Usual treatment for stroke. Drs asked to prescribe other VTE prophylaxis as per their usual practice for both groups (n=1562) Intervention 2: Anti-embolism stockings - Below knee. dose/quantity, brand name, extra details. Duration Up to 30 days. Concurrent medication/care: Usual treatment for stroke. Drs asked to prescribe other VTE prophylaxis as per their usual practice for both groups. Around 40% received some anticoagulant
Funding	Equipment / drugs provided by industry (Goverment funded, with stockings provided by Tyco Healthcare)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABOVE KNEE versus BELOW KNEE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Dead by 30d at 30 days from intervention; Group 1: 182/1552, Group 2: 174/1562; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler)

Study	Dennis 2010: CLOTS2 trial: Clots (clots in legs or stockings after stroke) trial collaboration 2010[56]
ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: Any DVT (proximal or distal, symptomatic or asymptomatic) confirmed by compression doppler ultrasound at 30 days from intervention; Group 1: 177/1552, Group 2: 211/1562; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: Pulmonary emboli confirmed by imaging or at autopsy at 30 days from intervention; Group 1: 23/1552, Group 2: 19/1562; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Technical complications of mechanical interventions at up to 90 days from hospital discharge - Actual outcome: Stocking removed due to concern about skin at 30 days from intervention; Group 1: 61/1552, Group 2: 75/1562; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Stocking removed due to patient reported discomfort at 30 days from intervention; Group 1: 127/1552, Group 2: 77/1562; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: DVT (symptomatic) - Actual outcome: Symptomatic DVT (proximal or distal) confirmed by compression doppler ultrasound at 30 days from intervention; Group 1: 85/1662, Group 2: 87/1562; Protocol outcome 6: DVT (proximal) - Actual outcome: Proximal DVT (symptomatic or asymptomatic) confirmed by compression doppler ultrasound at 30 days from intervention; Group 1: 98/1552, Group 2: 138/1562;	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge;

Study	CLOTS 3 trial: Clots (clots in legs or stockings after stroke) trials collaboration 2013 [82]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2876)
Countries and setting	Conducted in United Kingdom; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 30 days with f/u at six months.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed using compression duplex ultrasound, PE confirmed using imaging, skin breaks/ulcers/blisters/ skin necrosis confirmed using imaging
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Pre-specified subgroups (all dichotomous): Randomisation more than 1 day after admission; randomisation more than 2 days after onset of stroke; Heparin, warfarin or alteplase used; Can lift both legs off the bed; Probability of a favourable outcome; High risk DVT; Haemorrhagic stroke; "Comfort" sleeve in stocking.
Inclusion criteria	Admitted into hospital within 3 days of acute stroke, cannot mobilise to toilet unaided.
Exclusion criteria	Age <16y, subarrachnoid haemorrhage, contraindications to intermittent pressure compression such as dermatitis, leg ulcers, severe oedema, severe peripheral vascular dx, and congestive heart failure.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Median (IQR): 76.5 (67-84). Gender (M:F): 1383:1493. Ethnicity: Not reported
Further population details	1. BMI : Not stated 2. Renal impairment: Not stated 3. Type of stoke: Mixed (13% confirmed haemorrhagic, not reported separately).
Indirectness of population	No indirectness
Interventions	(n=1438) Intervention 1: Intermittent pneumatic compression devices - Full leg. Kendall SCD express sequential compression system (Covividium) thigh-length, applied according to manufacturer's instructions to both legs. Worn 24/7. Duration Up to 30 days, regain mobility or discharge from hospital. Concurrent medication/care: Physicians requested to prescribe medical VTE prophylaxis as if no stockings, according to their usual practice. Comments: 58% participants had standard sleeves, but "comfort" sleeves in second half of trial. (n=1438) Intervention 2: No treatment - Usual care. No intermittent compression stockings. Duration 30 days or until discharged. Concurrent medication/care: Physician asked to prescribe VTE prophylaxis according to their usual practice.

Study	CLOTS 3 trial: Clots (clots in legs or stockings after stroke) trials collaboration 2013 [82]
Funding	Equipment / drugs provided by industry (Study funding from National Institute of Health Research (NIHR), Health Technology Assessment programme (HTA) and Scottish Government. Equipment donated by Covidien.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FULL LEG IPC versus USUAL CARE Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: Dead at 30 days; Group 1: 156/1438, Group 2: 189/1438; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: Any DVT at 30 days; Group 1: 233/1438, Group 2: 304/1438; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: All confirmed pulmonary embolism at 30 days; Group 1: 29/1438, Group 2: 35/1438; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Technical complications of mechanical interventions at up to 90 days from hospital discharge - Actual outcome: Skin breaks at 30 days; Group 1: 44/1438, Group 2: 20/1438; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: DVT (symptomatic) - Actual outcome: Symptomatic DVT (proximal or calf) at 30 days; Group 1: 66/1438, Group 2: 90/1438; Protocol outcome 6: DVT (proximal) - Actual outcome: Proximal DVT at 30 days; Group 1: 122/1438, Group 2: 174/1438;	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-

Study	CLOTS 3 trial: Clots (clots in legs or stockings after stroke) trials collaboration 2013 [82]
	induced thrombocytopenia at up to 90 days from hospital discharge;

Study	Duke 1983[89]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=65)
Countries and setting	Conducted in Canada; Setting: Two hospitals (names not reported)
Line of therapy	Not applicable
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): defined by fibrinogen leg scanning
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with "partial stable stroke". Presence of focal cerebral neurological deficit, of presumed vascular origin; minor or moderate severity (≥5 MRC units combined upper and lower limb proximal strength on weaker side); deficit began within 48 hours of presentation; no alteration of consciousness.
Exclusion criteria	Sustained hypertension (diastolic blood pressure >110 mmHg); clear evidence of cardiac embolism; haemorrphagic diathesis; active peptic ulcer within 2 years; patients on anticoagulant therapy; fever > 38.5·C; CT scan incompatible with cerebral infarction; >200 RBC/ml in CSF; preexisting neurological deficit
Recruitment/selection of patients	14-month period (dates not reported). Patients were randomised within 48 hours onset of stroke.
Age, gender and ethnicity	Age: Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. BMI: Not applicable 2. Renal impairment: Not applicable 3. Type of stoke: Not applicable
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH, 5000IU was subcutaneously administered every 8 hours (three times daily). Duration 7 days. Concurrent medication/care: n/a. Indirectness: No indirectness (n=30) Intervention 2: No treatment - Placebo. Placebo, no further details reported. Duration 7 days. Concurrent medication/care: n/a. Indirectness: No indirectness

Study	Duke 1983[89]
Funding	Academic or government funding (Supported by grants from Ontario and Canadian Heart Foundations)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN versus PLACEBO Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 7 days; Group 1: 0/35, Group 2: 3/30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge;

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Diener et al., 2006 [85] (PROTECT	Patient group: Acute ischaemic stroke Setting: 37 centres in EU, most patients	Group 1 UFH 5000IU, 3 times daily,	All-cause mortality (confirmed by: Autopsy whenever allowed. Stroke	Treatment period Group1: 7/273 Group 2: 7/ 272 P value: 1.0	Funding: Novartis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
trial) Country of study: EU Study design: RCT, double blinded, multicentre List who was masked to interventions : Investigators and patients. End point committee Evidence level: 1+ Duration of follow-up: 3 months	treated in stroke units Inclusion criteria: Age 18 to 85 years with clinical diagnosis of ischaemic stroke NIHSS score of 4 to 30, with mild to severe paresis of a leg. Exclusion criteria: Indication of thrombolysis No availability of CT scan Ct documented signs of intracerebral or subarachnoid bleeding Current bleeding or thrombosis History of bleeding or thrombosis within the past 12 months Recurrent gastrointestinal ulcerations Post thrombotic syndrome Acute or unstable cardiovascular disease Major infection Currently active, recurrent or metastatic cancer within the last 5 years Platelet count <75000/microL Severe diabetic retinopathy Estimated body weight <55jg Pregnant or breast feeding All patients N: 545 Group 1	subcutaneously Start: 15.4±6.2 Group 2 Certoparin 3000U anti Xa once daily, subcutaneously, plus 2 placebo injections Start: 15.4±6.2 All treatment started within 24 hours of stroke symptom onset Duration: 12-16 days Additional non-comparative prophylaxis: Ticlopidine, clopidogrel, or aspirin alone (≤325mg daily) or in combination with dipyramidole allowed Aspirin	progression as cause of death: n=4 in certoparin, n=3 in UFH during treatment period. At 3 month follow up, n=3 in certoparin, n=1 in UFH)	Between treatment period and 3 month follow up: Group1: 8/273 Group 2: 14/ 272 P value: 0.2 Total: up to 3 month follow up: Group1: 15/273 Group 2: 21/ 272 P value: 0.31 [p values calculated by team at NCCAC suing Fisher's exact test]	Limitations: Percentages of patients with concurrent antiplatelet agents were not reported Seemed to have involved both stroke unit centres and non-stroke unit centres- outcomes not compared Outcomes not reported: Calf DVT, PTS, Pulmonary hypertension, QoL, LOS Additional outcomes reported: Causes of death Notes: Patients screened for DVT at baseline with duplex and compression
			Fatal pulmonary embolism (confirmed by: Not autopsy performed. Suspected, because D-dimer positive but no signs of cardiac aetiology found)	Group1: 1/273 Group 2: 0/272 P value: 1.0 [p values calculated by team at NCCAC suing Fisher's exact test]	
			Symptomatic pulmonary embolism (confirmed by: no clinically suspected PE)	Group1: 1/273 Group 2: 0/272 P value: 1.0 [p values calculated by team at NCCAC suing Fisher's exact test]	
			Proximal DVT, asymptomatic or symptomatic	Group1: 23/273 Group 2: 18/272 P value: 0.52	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 273 Per protocol: 248 M/F: 164/109 Age (mean +SD): 67.3 +10.6 Additional characteristics: • Body Mass Index: 27.1±3.9 • NIHSS: 8.2±3.6 • Leg paresis:2.0±0.9 ○ Grade 1:91 ○ Grade 2:110 ○ Grade 3:55 ○ Grade 4:17 • Infarction in carotid territory:251 • Previous stroke:37 • Previous transient ischaemic attack: 7 • Hypertension:207 • Previous cardiac failure:8 • Previous myocardiac infarction:15 • Diabetes mellitus:71 • Hyperlipidaemia: 48 • Previous severe respiratory disorder:13 • Previous thrombosis:9 Group 2 No. randomised: 272 Age (mean +SD): 66.3 +10.9 Per protocol: 242 M/F: 149/123 Additional characteristics:	Group 1:78.4% Group 2:77.2% Aspirin + dipyramidole Group 1:11.7% Group 2:17.6% Clopidogrel Group 1: 17.6% Group 2: 16.9% Ticlopidine Group 1: 4.4% Group 2: 2.9% No mention of mechanical prophylaxis methods	(confirmed by: Duplex and compression ultrasonography. Routinely scanned at Days 3-4, 7-8, 12-16 and when clinical symptoms occurred)	[p values calculated by team at NCCAC suing Fisher's exact test] Note: all were reported as proximal DVT	ultrasonography.
			Fatal bleeding (description: 1 intracranial bleeding was confirmed by autopsy-during treatment period. At 3 month follow up, 1 severe bleeding in the UFH group was confirmed by autopsy. The bleeding type of the LMWH group was not reported)	During treatment period Group1: 1/ 273 Group 2: 0/ 272 P value: Between treatment period and 3 month follow up: Group1: 1/ 273 Group 2: 1/272 P value: [p values calculated by team at NCCAC suing Fisher's exact test]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

	• Body Mass Index: 27.4±4.6
	• NIHSS:8.7±4.0
	• Leg paresis: 2.1±0.9
	  ○ Grade 1:86
	  ○ Grade 2:108
	  ○ Grade 3:55
	  ○ Grade 4:23
	• Infarction in carotid territory:256
	• Previous stroke:42
	• Previous transient ischaemic attack:10
	• Hypertension:210
	• Previous cardiac failure:21
	• Previous myocardiac infarction:23
	• Diabetes mellitus:81
	• Hyperlipidaemia: 51
	• Previous severe respiratory disorder:20
	• Previous thrombosis:6				

			Major bleeding at 16 days (description: intracranial (only if parenchymal), retroperitoneal, gastrointestinal resulted in death, clinically overt and led to transfusion of ≥U of packed RBC/whole blood, or Hb fall of ≥2g/dL)	Group1: 5/273 Group 2: 3/272 P value: 0.73 [p values calculated by team at NCCAC suing Fisher's exact test]	
			Neurological bleeding CT scan performed at	Group1: 3/273 Group 2: 2/272	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			baseline, Days 7 to 8 routinely and anytime in the case of clinical suspicion of intracranial haemorrhage	P value: 1.0 [p values calculated by team at NCCAC suing Fisher's exact test]	
			Upper GI bleeding	Group1: 2/273 Group 2: 0/272 P value: 0.5	
			Minor bleeding (description: bleedings which did not meet classification of major bleeding)	Group1: 5/273 Group 2: 7/ 272 P value: 0.58 [p values calculated by team at NCCAC suing Fisher's exact test]	
			Heparin induced thrombocytopaenia (suspected cases, not measurement of antibodies performed to confirm)	Group1: 2/273 Group 2: 1/ 272 P value: 1.0 [p values calculated by team at NCCAC suing Fisher's exact test]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Hillbom et al., 2002 [147] Country of study: Finland	Patient group: Acute ischaemic stroke Setting: 7 centres in Finland. Inpatient	Group 1 Unfractionated heparin, 5000IU, subcutaneously, 8 hourly. Group 2	All-cause mortality 16/17 patients died of stroke within treatment period, 22/32 during the follow up period	Within treatment period (10±2 days) Group1: 8/106 Group 2: 9/106 P value: 1.00 [Calculated by NCC-AC team using Fisher's Exact test]	Funding: Aventis Pharma Limitations: Sample size of 400 was planned, but only 212 recruited

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: Multicentre, double blinded, randomised study List who was masked to interventions: Double blinded study Evidence level: 1+ Duration of follow-up: 3 months	Inclusion criteria: Acute ischaemic stroke, defined as acute onset of paralysis lasting at least 24 hours and necessitating bed rest Confirmed by CT scan Exclusion criteria: Unconscious- Glasgow Coma Scale <9 Immobilised before onset of stroke Evidence of haemorrhagic stroke Stroke thought to be cardioembolic in origin History of DVT, PE myocardial infraction, recent neurosurgery (within the last 3 months) History of subarachnoid haemorrhage, gastrointestitinal bleeding or active peptic ulceration Hypersensitivity to heparin, LMWH or radio opaque contrast media Severe heart failure, uncontrolled hypertension, hepatic or renal impairment, malignant disease, endocarditis or haemorrhagic diathesis Current drug abuse Requiring anticoagulant or antiplatelet therapy Pregnant or lactating Abnormal blood clotting tests Treatment would not be started with 48 hours of stroke onset	Enoxaparin (Clexane), 40mg, subcutaneously, once daily. 2 placebo injections to maintain 8 hourly interval blinding. In both arms Start time: within 48 hours of stroke onset End time: 10±2 days later, or until discharge Additional non-comparative prophylaxis: Concomitant treatment with anticoagulant or antithrombotic therapy, NSAIDS, aspirin or other antiplatelet therapy, or any other treatment which could influence interpretation of		At 3 month follow up Group1: 28/106 Group 2: 21/106 P value: 0.33 [Calculated by NCC-AC team using Fisher's Exact test]	and 165 patients (81 in enoxaparin and 84 in UFH) group completed study NO mention about mechanical prophylaxis methods Significantly more obese patients in UFH group and higher percentages of diabetic patients Outcomes not reported: Upper GI bleeding Additional outcomes reported: Haemorrhagic transformation of the brain infarction Notes: # The number of DVT cases reported was
			Fatal pulmonary embolism (confirmed by: autopsy) Of all the patients who died, 14 had autopsy. 4 in UFH and 2 in enoxaparin group had PE	Group1: 2/106 Group 2: 1/106 P value: 0.62 [Calculated by NCC-AC team using Fisher's Exact test]	
			Symptomatic pulmonary embolism (ventilation perfusion scan and pO2 when clinically indicated)	Group1: 4/106 Group 2: 2/106 P value: 0.68 [Calculated by NCC-AC team using Fisher's Exact test]	
			Symptomatic DVT (confirmed by: unilateral phlebography within 24h of clinical indication)	Group1: 3/ 72 Group 2: 1/ 76 P value: 0.36 [Calculated by NCC-AC team using Fisher's Exact test]	
			DVT, asymptomatic or symptomatic (confirmed by: as in symptomatic DVT, and bilateral ascending phlebography at day 10±2 or the last assessment, and	Group1: 24/106 Group 2: 14/106 P value: 0.17 (# see notes) [Calculated by NCC-AC team using Fisher's Exact test]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients N: 212 Group 1 No. randomised: 106 Efficacy population: 72 No. of dropouts: 0 M/F: 59/47 Age: 69±10 Weight (kg): 77±16 Risk factors for DVT: Elderly (>70 years):48/106 Immobilised: 104/106 *Obesity: 28/106 *Alcoholism: 4/106 Varicose veins: 10/106 History of DVT: 3/106 Risk factors for Stroke: Hypertension: 48/106 Current smoking: 25/106 *Diabetes mellitus: 21/106 History of myocardial infarction: 5/106 History of stroke or TIA: 5/106 Group 2 No. randomised: 106 Efficacy population: 76 No. of dropouts: 0 M/F: 68/38 Age: 68±12 Weight (kg):73±13 Risk factors for DVT:	study data was prohibited. No mention about mechanical prophylaxis methods	autopsy)		26/106 in the UFH group and 17/106 in the LMWH group respectively. However, 2 cases in the UFH group and 3 in the LMWH group were detected after the study period. These cases were excluded. Patients were analysed using both randomised number, and the efficacy subgroup
			Thigh (Proximal) DVT(confirmed by: as in DVT)	Group1: 4/72 Group 2: 2/76 P value: 0.43 [Calculated by NCC-AC team using Fisher's Exact test]	
			Calf (Distal)DVT (confirmed by: As in DVT)	Group1: 3/72 Group 2: 1/76 P value: 0.36 [Calculated by NCC-AC team using Fisher's Exact test]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Elderly (>70 years):53/106 Immobilised: 101 /106 *Obesity: 10/106 *Alcoholism: 12/106 Varicose veins: 10/106 History of DVT:3/106 Risk factors for Stroke: Hypertension: 45/106 Current smoking: 28/106 *Diabetes mellitus: 12/106 History of myocardial infarction: 7/106 History of stroke or TIA: 8/106 * Obesity (p=0.002) , diabetes (p=0.13), alcoholism (p=0.066) [Values calculated by NCCAC staff using Fisher‟s exact test]				
			Fatal bleeding (description: autopsy)	Of the patients who died, 14 had autopsy. 1 in enoxaparin group had cerebral haemorrhage	
			Major bleeding (description: intracranial haemorrhage)	Group1: 0/106 Group 2: 1/106 P value:	
			Neurological bleeding (intracerebral haemorrhage) confirmed by cerebral CT scan, within 24 hours of clinical indication and within 24 hours of the final administration	Group1: 0/106 Group 2: 1/106 P value: 1.0 [Calculated by NCC-AC team using Fisher’s Exact test]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Neurological bleeding (Haemorrhagic transformation of the brain infarction) Confirmed by CT scan within 24 hours of final administration	Group1: 20/86 Group 2: 14/81 P value: 0.44 [Calculated by NCC-AC team using Fisher's Exact test]	
			Minor bleeding (description: included 3 in enoxaparin and 4 in UFH with hematomas>5cm in diameter at injection site)	Group1: 6/106 Group 2: 5/106 P value: 1.00 [Calculated by NCC-AC team using Fisher's Exact test]	

Study	Lacut 2005[182]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in France; Setting: Brest University Hospital, France
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by compression ultrasonography
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged over 18 years, traumatic or spontaneous intracerebral haemorrphage with or without subarachnoidal haemorrphage, and written informed consent given by the patient or relative
Exclusion criteria	Extra- or subdural haematomas, traumatic intracerebral haemorrphage due to polytrauma including the lower limbs, haemorrphagic transformation of ischemic infarct and vasculitis (when the diagnostic was established), patients or

Study	Lacut 2005[182]
	relative refusal, a deep vein thrombosis (DVT) within the previous 3 months, a lower-limb arteriopathy with an ankle-to-arm systolic pressure index <0.70, a venous graft, a wound in the lower limb related either to a vascular disease (ulcer) or a trauma, a "do not resuscitate" order, and a >24 hour delay since hospital admission.
Recruitment/selection of patients	Between February 2002 and December 2003
Age, gender and ethnicity	Age - Mean (SD): 62.8 (13.7) years. Gender (M:F): 1.4/1. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable 3. Type of stoke: Not applicable
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Intermittent pneumatic compression devices - Full leg. IPCD (length not specified) in combination with anti-embolism stockings (length not specified). The graded elastic stockings were put on as soon as patients were admitted to standard care. The compression device (three chambers) was applied sequentially for 11 seconds with pressures of 45, 40 and 30 mmHg at the ankle, calf, and thigh. Duration: Duration is unclear. Concurrent medication/care: N/A. Indirectness: No indirectness (n=77) Intervention 2: Anti-embolism stockings - Mixed above/below knee. Patients received anti-embolism stocking (length not specified). The graded elastic stockings were put on as soon as patients were admitted to standard care. Duration: Duration is unclear. Concurrent medication/care: N/A. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Tyco Healthcare France provided all of the mechanical devices (elastic graded stockings and intermittent pneumatic compression system.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IPCD + GRADED ELASTIC STOCKINGS versus GRADED ELASTIC STOCKINGS

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at time-point not reported; Group 1: 15/74, Group 2: 24/77
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: n/a; Group 2 Number missing: 0, Reason: n/a

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at time-point reported; Group 1: 3/64, Group 2: 11/69
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: Death; Group 2 Number missing: 8, Reason: Death

Study	Lacut 2005[182]
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge;

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
McCarthy et al., 1977 [220] Country of study: UK Study design: RCT List who was masked to interventions: No one	Patient group: Stroke Patients Setting: Department of Geriatric Medicine Inclusion criteria: Diagnosis of stroke within previous 48 hours Exclusion criteria: ■ Blood in the cerebrospinal fluid (defined as 50 red cells per high-power field in tube 3 of a lumber puncture) ■ Sustained diastolic blood pressure higher than 120mmHg on admission or grades 3 or 4	Group 1 Unfractionated Heparin (calcium) Start time: Unclear Duration: 14 days Dose and frequency: 5000U subcutaneously every 8 hours Group 2 No heparin	All-cause mortality	Group1: 3/16 Group 2: 5/16 P value: 0.685*	Funding: No information provided Limitations: No information is provided about the method of randomisation or allocation concealment. Trial is not blinded and few baseline characteristics are provided.
			DVT, asymptomatic or symptomatic (confirmed by: Radiofibrinogen uptake test)	Group1: 2/16 Group 2: 14/16 P value: 0.001*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Evidence level: 1+ Duration of follow-up: 14 days for DVT 28 days for Death	hypertensive retinopathy; History of active peptic ulceration; History of subarachnoid haemorrhage; Allergy to iodine; Goitre or thyrotoxicosis; Bleeding diathesis; Recent Myocardial infarction; or All patients N: 32 Age (mean): Gp1: 78.9 (S.D 8.0) Gp2: 78.2 (SD 7.4) M/F: 11:21 Additional risk factors: Mean Severity: Gp1: 4.3 ± 1.8 Gp2: 3.4 ± 21.6 Group 1 No. randomised: 16 No. of dropouts: 0 Group 2 No. randomised: 16 No. of dropouts: 0	Additional non-comparative prophylaxis: None listed			Pilot study for MCCARTHY1986 Outcomes not reported: Fatal PE, Symptomatic PE, Symptomatic DVT, Bleeding, Heparin induced thrombocytopaenia, Pulmonary hypertension, Post thrombotic syndrome, quality of life, length of stay. Additional outcomes reported: None Notes: * Calculated by NCC team using Fisher Exact Test.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
McCarthy & Turner, 1986 [219] Country of study: UK Study design: RCT List who was masked to interventions: No one Evidence level: 1+ Duration of follow-up: 14 days for DVT 12 weeks for death	Patient group: Stroke Patients Setting: Department of Geriatric Medicine Inclusion criteria: Diagnosis of stroke within previous 48 hours Exclusion criteria: ■ Sustained diastolic blood pressure higher than 120mmHg on admission or grades 3 or 4 hypertensive retinopathy; ■ History of active peptic ulceration; ■ History of subarachnoid haemorrhage; Allergy to iodine; Goitre or thyrotoxicosis; Bleeding diathesis; Recent Myocardial infarction; or ■ Diagnosed malignancy All patients N: 305 Age (mean): 76 (S.D 8.1)	Group 1 Unfractionated Heparin (calcium) Start time: Unclear Duration: 14 days Dose and frequency: 5000U subcutaneously every 8 hours Group 2 No heparin Additional non-comparative prophylaxis: None listed	All-cause mortality DVT, asymptomatic or symptomatic (confirmed by: Radiofibrinogen uptake test)	Group1: 31/144 Group 2: 53/161 P value: 0.029* Group1: 32/144 Group 2: 117/161 P value: <0.001*	Funding: Chest Heart and Stroke association, Oxford locally organised research funds and Labaz & Evans biologicals Limitations: No information is provided about the method of randomisation or allocation concealment. Trial is not blinded and few baseline characteristics are provided. Outcomes not reported:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 132:173 Additional risk factors: Mean Severity: Gp1: 4.4 ± 2.38 Gp2: 4.8 ± 2.65 Group 1 No. randomised: 144 No. of dropouts: Unclear Group 2 No. randomised: 161 No. of dropouts: Unclear				Fatal PE, Symptomatic PE, Symptomatic DVT, Bleeding, Heparin induced thrombocytopenia, Pulmonary hypertension, Post thrombotic syndrome, quality of life, length of stay. Additional outcomes reported: Pulmonary embolism at post mortem (not fatal

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Muir et al., 2000 [232] Country of study: UK Study design: RCT List who was masked to interventions: Outcome assessment was masked Evidence level: 1+ Duration of follow-up: 7 days (+/- 2 days)	Patient group: Stroke patients within 72 hours of stroke onset Setting: Acute stroke unit Inclusion criteria: ■ Clinically diagnosed acute stroke not independently ambulant within 24hours of admission ■ Leg weakness of National Institutes of Health Stroke Scale (NIHSS) 1 Exclusion criteria: Coma patients Life threatening intercurrent illness Critical lower-limb ischaemia Severe dermatological conditions All patients N: 97 Age (mean): 76 M/F: NR Additional risk factors: For VTE Hypertension: 43/97 Ischaemic heart disease: 29/97 Previous stroke or TIA: 27/97 Smoker: 28/97 Diabetes: 8/97 Personal history of VTE: 4/97	Group 1 Standard care + leg length graduated compression stockings. Either Kendall TED (37 patients) or Brevet TX (28 patients). Compression profiles not reported. Start time: NR End time: NR Duration: 7 days Group 2 Standard care includes CT scanning or MRI, aspirin, IV fluids or those unable to swallow and early mobilisation within 24 hours of admission. Start time: NR End time: NR Duration: 7 days Additional non-comparative	All-cause mortality (study does not report how outcome was confirmed)	Group1: 9/65 Group 2: 4/32 P value: NR in study but calculated by NCC- AC as p = 1.00 (Fishers exact test)	Funding: Stroke Association Outcomes not reported: Fatal PE Symptomatic PE Symptomatic DVT Thigh DVT Calf DVT Fatal Bleeding Major Bleeding Neurological Bleeding Upper GI Bleeding Minor Bleeding Heparin induced thrombocytopaenia Post thrombotic syndrome Pulmonary hypertension Quality of life Length of stay Additional outcomes reported: Proximal DVT Group1: 3/65
			Pulmonary embolism, asymptomatic or symptomatic (study does not report how outcome was confirmed)	Group1: 0/65 Group 2: 0/32 P value	
			DVT, asymptomatic or symptomatic detected within the first seven days (confirmed by Acuson 128 colour-flow Doppler ultrasound with motion discrimination software)	Group1: 7/65 Group 2: 7/32 P value: NR in study but calculated by NCC- AC as p = 0.21 (Fishers exact test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Familial history of VTE: 1/97 Stroke categories: Oxford Community Stroke Project Scale (OCSP) Total Anterior Circulation Stroke: 29/97 Partial Anterior Circulation Stroke: 31/97 Lacunar Circulation Stroke: 21/97 Posterior Circulation Stroke: 8/97 Group 1 No. randomised: 65 (37 Kendall TEDs + 28 Brevet TX) No. of dropouts: 19 (29%) [11 TX and 8 in TED] 3 patients were intolerant to stockings 4 withdrew for unstated reasons 2 protocol violations where stockings were not worn as intended Age (mean): 76 (TED) 73 (TX) M/F: NR Additional risk factors: For VTE Hypertension: 15/28 (TX) 14/37 (TED) Ischaemic heart disease: 9/28 (TX) 11/37 (TED) Previous stroke or TIA: 10/28 (TX) 8/37 (TED) Smoker: 10/28 (TX) 9/37 (TED)	prophylaxis: Aspirin – dose not stated as standard stroke treatment			Group 2: 2/32 DVT at 1st examination DVT at 2nd examination Notes: Computer generated randomisation with numbers placed in sealed envelopes (opacity of envelopes was not mentioned so possibly introducing selection bias). Power calculation assuming 50% DVT incidence and 50% relative risk reduction. The study had 80% power to detect this difference at 5% significance with 100 patients randomised in a 2:1 ratio of stockings to standard treatment.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Diabetes: 2/28 (TX) 3/37 (TED) Personal history of VTE: 1/28 (TX) 3/37 (TED) Familial history of VTE: 1/28 (TX) 0/37 (TED) Stroke categories: Oxford Community Stroke Project Scale (OCSP) Total Anterior Circulation Stroke: 9/28 (TX) 9/37 (TED) Partial Anterior Circulation Stroke: 7/28 (TX) 13/37 (TED) Lacunar Circulation Stroke: 6/28 (TX) 10/37 (TED) Posterior Circulation Stroke: 4/28 (TX) 2/37 (TED) Group 2 No. randomised: 32 No. of dropouts: 6 (19%) Age (mean): 76 M/F: NR Additional risk factors: For VTE Hypertension: 14/32 Ischaemic heart disease: 9/32 Previous stroke or TIA: 9/32 Smoker: 9/32 Diabetes: 3/32 Personal history of VTE: 0/32 Familial history of VTE: 0/32				1070 screened for potential inclusion, 953 (89%) excluded and 19 (2%) non-compliant. Reasons for exclusion: mobile / discharged 537, amputee 12, consent refused or unobtainable 77, coma / poor prognosis 66, peripheral vascular disease 4, dermatological (incl. MRSA) 19, non-stroke diagnosis 20, other clinical trial 59, technical / admin 17, already using stockings 34 and other 108. Of the 98 recruited one had „clinically manifest DVT during the study period and was not included in the results.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Stroke categories: Oxford Community Stroke Project Scale (OCSP) Total Anterior Circulation Stroke: 11/32 Partial Anterior Circulation Stroke: 11/32 Lacunar Circulation Stroke: 5/32 Posterior Circulation Stroke: 2/32 No significant difference in any demographic, stroke characteristics or dropout rates between the two groups.				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pambianco et al., 1995 [250] Country of study: USA Study design: RCT List who was masked to interventions: No one	Patient group: Stroke patients (not necessarily newly defined) Setting: Rehabilitation centre Inclusion criteria: All cases with a diagnosis of non-haemorrhagic stroke identified by CT scan in the referring hospital and who have a paralysed or severely weakened lower limb. Exclusion criteria: Patients on anticoagulation therapy	Group 1 No prophylaxis Group 2 Standard Sodium Heparin (no brand name) Start time: 1st full day at centre End time: day 28 Duration: 28 days or discharge Dose and frequency: 5,000U every 8 hours, adjusted in 500U	All-cause mortality	Group 1: 0/115 Group 2: 0/120 Group 3: 0/117	Funding: US department of Education Limitations: No details of randomisation provided No blinding of analysts not mentioned High patient dropout rates for heparin and IPCD group. Outcomes not reported: All-cause
			DVT, asymptomatic or symptomatic (screened for by: B-mode 2-dimensional imaging and pulsed doppler ultrasound at or above the popliteal vein twice a week until the completion of the study or discharge.)	Group1: 6/115 (completed study) Group 2: 5/120 (completed study) Group 3: 8/117 (completed study) P value: NR Grp 1 v Grp 2 = 0.76 Grp 1 v Grp 3 = 0.78 Grp 2 v Grp 3 = 0.41 2-sided Fisher's exact test calculated by NCC- AC using ITT original numbers randomised	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Evidence level: 1+ /- ? Duration of follow-up: 28 days	haemorrhagic stroke more than 10 weeks after stroke active cancer „other medical contraindications" including dementia, amputation, stroke not identifying specific area Contraindications to heparin diabetic ulcers. All patients N: 360 randomised – overall baseline data provided for only those completing study Age (mean): 72.2 ± 9.5 M/F: 41/59 Additional risk factors: BMI: 26.1 ± 5.7 Time from stroke to admission: 24.2 days Group 1: No prophylaxis No. randomised: 115 No. of dropouts: 9 (8%) Group 2 (Heparin) No. randomised: 120 No. of dropouts: 30 (25%) Group 3 (IPCD) No. randomised: 117	increments to maintain daily PTT between 30.0 – 39.9. Maximum dose 10,000U every 8 hours Group 3 IPCD – Anti-thrombic pump (double lined stoking containing inflatable bladder) Start time: 1st full day at centre End time: day 28 Duration: 8 hours each night Length and compression profile: below knee. Group 4 Mederomic Functional Electrical Stimulation Device				mortality, PE (any type), Symptomatic DVT, Calf DVT, Thigh DVT, Bleeding (any type), HIT, PTS, Pulmonary Hyper tension, QoL, LoS Additional outcomes reported: Adverse events for heparin included: echymotic area over abdomen and areas distal to injection site. 10 point decrease in haematocrit level; nausea and vomiting with onset of heparin therapy, bleeding from the ear, haematochezia, haemepositive stools, bleeding around tracheal stoma, thrombocytopaenia Adverse events for IPCD,

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. of dropouts: 26 (22%) Group 4 (Functional Electrical Simulation) No. randomised: 8 No. of dropouts: 6 (75%) Study arm discontinued	(discontinued due to adverse events) Additional non-comparative prophylaxis: All patients received bilateral below knee stockings (no compression).			bilateral skin changes Notes: High dropout rate in IPCD due to disruption of sleep. 21 patients were transferred to acute care for complications unrelated to study treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Prasad et al., 1982 [267] Country of study: UK Study design: RCT List who was masked to interventions:	Patient group: Stroke Setting: Geriatric ward Inclusion criteria: ■ All patients admitted for acute stroke within 72 hours ■ Anyone with weakness up to 2/6 motor power (MRC grade) in one or both limbs on either side Exclusion criteria: ■ Patients in a coma or with another clinically unacceptable	Group 1 Intermittent pneumatic calf compression with Flowtron legging at 40 mmHg to both legs, each cycle lasts 4 minutes. Treatment continuous for 24 hours then for periods of 3 hours, 3/day for next 9 days.	DVT, asymptomatic or symptomatic (screened for by daily FUT scanning)	Group1: 6/13 Group 2: 6/13 P value: NR	Funding: Not reported Limitations: Randomisation method not explained Allocation concealment not mentioned. Blinding of investigators not mentioned. Outcomes not reported: All-cause mortality Fatal PE Symptomatic PE Symptomatic or asymptomatic

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
None mentioned Evidence level: 1+ Duration of follow-up: 10 days	condition All patients N: 26 Age (mean): NR Age group 1 = 78 ± 4 Age group 2 = 80 ± 6 M/F: 12/14 Additional risk factors: NR Group 1 No. randomised: 13 No. of dropouts: 2 patients died but data from autopsy were included Group 2 No. randomised: 13 No. of dropouts: 0	Duration: 10 days Group 2 No intervention Additional non-comparative prophylaxis: Not Applicable			PE Symptomatic DVT Thigh DVT, Calf DVT Fatal bleeding, Major bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding HIT, Post thrombotic syndrome, Pulmonary hypertension Quality of life, Length of Stay

Study	Prins 1989[268]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Netherlands; Setting: Department of Medicine, Bergweg Municipal Hospital, Rotterdam, The Netherlands
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by fibrinogen scan and unilateral phlebography

Study	Prins 1989[268]
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were only eligible if they entered within 72 hours of onset of symptoms, and were neither deeply comatose nor needing or using other anticoagulant therapy.
Exclusion criteria	No further details reported
Recruitment/selection of patients	Between June 1984 to January 1986
Age, gender and ethnicity	Age - Median (range): 76 years. Gender (M:F): 1/1. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable 3. Type of stoke: Ischemic
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Fragmin (dalteparin), 2500IU twice daily, subcutaneously administered. Duration 14 days. Concurrent medication/care: Usual care was given including early physical therapy. Indirectness: No indirectness (n=30) Intervention 2: No treatment - Placebo. Saline 0.9% was subcutaneously administered twice daily. Duration 14 days. Concurrent medication/care: Usual care was given including early physical therapy. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 14 days; Group 1: 9/30, Group 2: 4/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: n/a; Group 2 Number missing: 0, Reason: n/a

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 14 days; Group 1: 6/30, Group 2: 15/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: n/a; Group 2 Number missing: 0, Reason: n/a

Study	Prins 1989[268]
Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 14 days; Group 1: 1/30, Group 2: 2/30 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: n/a; Group 2 Number missing: 0, Reason: n/a	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge;

Study	Sandset 1990[286]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=103)
Countries and setting	Conducted in Norway; Setting: Department of Medicine, Aker University Hospital, Oslo, Norway (most patients were treated in a cerebrovascular care unit.
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days or until discharge from hospital, if earlier.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by venography and B-mode ultrasound scanning Major bleeding: defined as a fall in haemoglobin level of more than 20gm/litre, or led to blood transfusion, or was intracranial or fatal. Haemorrphagic transformation of brain infarction: confirmed by cerebral CT scan
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Sandset 1990[286]
Inclusion criteria	Patients admitted with clinical diagnosis of stroke.
Exclusion criteria	Haemorrphagic stroke diagnosed by obligatory cerebral computed tomography (CT) scan; stroke onset more than 72 hours before inclusion; strokes qualifying for treatment with heparin (hospital policy at the time was most patients with embolic and progressive strokes); known bleeding diathesis; severe hypertension (persistent diastolic blood pressure more than 120 mmHg or retinal haemorrphage or papilledema); severe renal failure (serum creatinine more than 300 µmol/litre) or hepatic failure (Normotest less than 40%); severe anaemia (haemoglobin less than 90 gm/liter) or thrombocytopenia (platelet count less than 80 x 10*9/litre); patients with malignancy disease and comatose patients.
Recruitment/selection of patients	Consecutive patients admitted with clinical diagnosis of acute stroke Recruitment from February 1986 to November 1988
Age, gender and ethnicity	Age - Mean (range): 75 (47-90) years. Gender (M:F): 1/1. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable 3. Type of stoke: Ischemic
Extra comments	Mean (range) weight of patients in study: 68 (40-112) kg
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin (Fragmin) was subcutaneously administered once daily, dose was adjusted according to body weight by the following regimen; less than 50kg, 0.30ml; 50-59 kg, 0.35ml; 60-69 kg, 0.40ml; 70-79kg, 0.45ml; 80-89kg, 0.50ml; more than 90 kg, 0.55ml. The patients in the active treatment group received 3000-5500 IU/day. The first injection was given subcutaneously at 4pm the day of randomisation followed by injections once daily at 9am. Duration 14 days or until discharge from the hospital if earlier. Concurrent medication/care: N/A. Indirectness: Serious indirectness; Indirectness comment: Dose is just outside of the standard dose range agreed for dalteparin (n=51) Intervention 2: No treatment - Placebo. No prophylaxis, 0.9% sodium chloride subcutaneously given once daily. Duration 14 days or until discharge from the hospital if earlier. Concurrent medication/care: N/A. Indirectness: No indirectness
Funding	Study funded by industry (Supported by grants from the Norwegian Council for Cardiovascular Diseases and by Kabi, Stockholm, Sweden)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (STANDARD DOSE) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge

Study	Sandset 1990[286]
- Actual outcome: All-cause mortality at 14 days; Group 1: 5/52, Group 2: 1/51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: n/a; Group 2 Number missing: 0, Reason: n/a Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 14 days; Group 1: 15/42, Group 2: 17/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: n/a; Group 2 Number missing: 1, Reason: n/a Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 14 days; Group 1: 0/52, Group 2: 0/51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: n/a; Group 2 Number missing: 0, Reason: n/a Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 14 days; Group 1: 0/52, Group 2: 1/51 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: n/a; Group 2 Number missing: 0, Reason: n/a Protocol outcome 5: Haemorrhagic transformation at up to 45 days from hospital discharge - Actual outcome: Haemorrphagic transformation at 14 days; Group 1: 4/50, Group 2: 3/52 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The number of patients reported in each arm for this outcome was clearly reported. There are two patients lost in the LMWH arm (total is 50). One patients is added to the placebo (total is 52). Rationale for this difference is not reported. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: n/a; Group 2 Number missing: 0, Reason: n/a	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital

Study	Sandset 1990[286]
	discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge;

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sherman et al., 2007 [296] Country of study: International: US, Europe and Asia Study design: RCT, non blinded List who was masked to interventions: Nil-Open label Evidence level: 1+ Duration of follow-up: Total of 90 days, 14 days	Patient group: Acute Ischaemic Stroke Setting: 200 centres in 15 countries Inclusion criteria: ≥18 years Acute ischaemic stroke confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) Unable to walk unassisted because of motor impairment, indicated by National Institute of Health Stroke Scale (NIHSS) ≥2 for motor function of leg Onset ≤ 48 hours of randomisation Exclusion criteria: Evidence of VTE at screening or active bleeding Evidence of history of intracranial haemorrhage, heparin induced or enoxaparin induced thrombocytopenia or thrombosis or both Hypersensitivity to iodinated contrast	Group 1 Unfractionated heparin (UFH), Dose/route: 5000U , subcutaneously, every 12h Start: within 48 hours Duration: 10±4days Group 2 Enoxaparin (Clexane) Dose/route: 40mg, subcutaneously, once daily Start: within 48 hours Duration: 10±4days Additional non-	All-cause mortality (up to Day 14 and 90 respectively)	Day 14 Group1: 45/872 Group 2: 48/877 P value: 0.58 Day 90 Group1: 103/872 Group 2: 100/877 P value:0.96 (P values were based on hazard ratio- log rank test)	Funding: Sanofi Aventis- funded and provided editorial support Limitations: Open label trial Safety (bleeding outcomes) not reported as stated in protocol-Minor extracranial haemorrhage (secondary safety outcome) not reported, "clinically important bleeding"- a post hoc definition was used No routine scanning of intracranial haemorrhage, a primary outcome. Use of mechanical prophylactic methods? Outcomes not reported: All-cause mortality at 48
			Fatal pulmonary embolism (up to 14 days, confirmed by autopsy)	Group1: 2/ 669 Group 2: 1/ 666 P value: 1.00 [Calculated by NCC-AC team using Fisher‟s Exact test]	
			Symptomatic pulmonary embolism (up to 14 days, confirmed by:)	Group1: 6/669 Group 2: 1/666 P value: 0.059	
			Symptomatic DVT (confirmed by: compression ultrasonography of the affected limb within 48 hours of symptom	Group1: 4/669 Group 2: 1/666 P value: 0.18 Note this was on efficacy group (screened), rather than randomised group	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
for main outcomes, 48 hours for bleeding events	media or iodine Spinal or epidural analgesia or lumbar puncture within the preceding 24 hours Thrombolytic treatment within the preceding 24hours Comatose at screening (NIHSS score ≥2 for level of consciousness) Known or suspected cerebral aneurysm or arteriovenous malformation Confirmed malignant disease that might have posed an increase risk of bleeding or compromise follow up or outcome assessment Impair haemostasis, e.g. baseline platelet count <100000 per microL, aPTT 1.5 times the laboratory upper limit of normal, INR>1.5 Major surgery or trauma within the preceding 3 months Expected need for full-dose treatment with therapeutic levels of an anticoagulant Treatment with LMWH or UFH at prophylactic dose for > 48h before inclusion Allergy or known hypersensitivity to heparin or enoxaparin Bacterial endocarditis Prosthetic heart valve Known or suspected anaemia (Hb<100g/L) Uncontrolled arterial hypertension (systolic blood pressure (BP) >180mmHg or diastolic	comparative prophylaxis: Mechanical prophylaxis not mentioned. Concomitant antiplatelet therapy was allowed. Number of patients receiving anti-platelet therapy: In the randomised group: At baseline: Enoxaparin: 825/884 (92%) UFH: 791/878 (90%) Received for >6 days after randomisation Enoxaparin: 82% 726/884 UFH group: 80% 698/878	onset) DVT, asymptomatic or symptomatic (up to 14 day, confirmed by: Asymptomatic patients confirmed by bilateral contrast venography within 72 hours of last dose of study medication. Ultrasonography used for patients who were unable to do venography) Proximal DVT(up to 14 days, confirmed by: see DVT) Distal DVT (up to 14days confirmed by: see DVT)	Group1: 118/669 Group 2: 67/666 P value:<0.0001 Note this was on efficacy group (screened), rather than randomised group Group1: 64/669 Group 2: 30/666 P value: 0.0003 Group1: 85/669 Group 2: 44/666 P value: 0.0002	hours, PE asymptomatic or symptomatic, Major bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding Heparin induced thrombocytopaenia, post thrombotic syndrome, pulmonary hypertension QoL, LOS Additional outcomes reported: Subgroup analysis by patient characteristics (forest plots) Outcomes by NIHSS score (by Day 14?) VTE NIHSS<14 Grp 1: 14.0%(10.91-17.02) Grp 2 : 8.3% (5.90-10.70) P value: 0.004 NIHSS ≥14 Grp 1: 29.7%(22.94-36.49) Grp 2 :16.3%(10.53-

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	BP>100mmHg) at randomisation or clinical hypertensive urgency Life expectancy <3 months due to comorbid disorders Participation in another clinical study within the preceding 30 days Any clinically relevant serious diseases, including severe liver disease or renal failure (creatinine clearance <30mL/min on ≥ 2 occasions) Female patients, if breast feeding, pregnant, or could become pregnant during the study All patients N: 1762 Characteristics: Group 1 Group 2 No randomised: 878 884 No dropouts: For safety population 6 7 For efficacy population 209 218 Age (years) 66.1±12.9 65.9±12.9 <65 372 371 65-75 265 312 >75 241 201 M/F 473/405 521/363 BMI (kg/m^3) 27.0±5.3 27.0±5.3 ≥30 183 179 Race: White 523 523 Black 55 68				21.97) P value: 0.004 DVT NIHSS<14 Grp 1: 13.6%(10.54-16.58) Grp 2 : 8.1%(5.73-10.48) P value: 0.005 NIHSS ≥14 Grp 1: 29.1%(22.41-35.88) Grp 2:16.3%(10.53-21.97) P value: 0.005 Clinically significant intracranial bleeding NIHSS<14 Grp 1: 0.3%(-0.12 to 0.77) Grp 2: 0.3% (-0.12 to 0.74) P value: 0.97 NIHSS ≥14 Grp 1: 1.6%(0.04 to 3.16) Grp 2:16.3%(-0.33 to 2.05) P value: 0.47

Study details	Patients		Interventions	Outcome measures	Effect size	Comments
	Asian	193 182				
	Hispanic	68 73				Major extracranial
	Others	39 38				NIHSS<14
	NIHSS score					Grp 1: 0%
	<14	626 648				Grp 2 : 0.5%(-0.06 to 0.99)
	≥14	252 236				P value: 0.09
	Motor leg function (NIHSS score):					NIHSS ≥14
	0	0 3				Grp 1: 0
	1	10 16				Grp 2: 1.7%(0.05-3.40)
	2	381 356				P value: 0.04
	3	293 316				Notes:
	4	387 193				Methodological paper published in year 2005
	Venous stasis syndrome	11 3				
	Varicosis	16 19				
	Previous VTE	14 16				
	Previous thrombolytic therapy	58 50				
	Concomitant antiplatelet:	791 815				
	Aspirin	738 767				
	Aspirin with dipyramidole	45 36				
	Clopidogrel	174 189				
	Dipyramidole	47 40				
	Ticlopidine	28 28				
	Other	56 52				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Fatal bleeding (description: within 48 hours of stopping treatment)	Group1: 4/872 Group 2: 5/877 P value: 1.0	
			Major bleeding (intracranial and extracranial)	Group1: 6/872 Group 2: 11/877 P value:0.33 [value calculated by NCC-AC team using Fisher's exact test]	
			Major (extracranial) bleeding (description: Within 48 hours of stopping treatment, overt bleeding resulting in either death, drop of Hb level of ≥30g/L, need for transfusion≥2 units of blood, surgical intervention or decompression of closed space to stop or control event, bleeding in retroperitoneal or intraocular location)	Group1: 0/872 Group 2: 7/877 P value: 0.015	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Neurological (Intracranial) bleeding (within 48 hours of stopping treatment, symptomatic, confirmed by head CT or MRI scan, or autopsy)	Group1: 6/872 Group 2: 4/877 P value: 0.55	
			Minor (extracranial) bleeding (within 48 hours of stopping treatment. Description: any clinically overt bleeding not meeting the criteria for major extracranial bleeding, and associated with at least one of the following: epistaxis lasting more than 5 minute or needing intervention, ecchymosis or haematoma >5 cm at its widest point, haematuria not associated with urinary catheter trauma, gastrointestinal haemorrhage not related to intubation of nasogastric tube placement, wound	Group1: 48/872 Group 2: 42/877 P value: 0.50	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			haematoma or haemorrhagic wound complications not associated with features of over haemorrhage classified as major or subconjuctival haemorrhage needing end of study treatment)		

Table 45: Average comparative outcomes with and without intermittent pneumatic compression (IPC) per 1000 patients who are immobile when admitted for stroke

		Standard best medical care (cases per 1000 patients)	Standard best medical care plus intermittent pneumatic compression (IPC) [a] (cases per 1000 patients, with 95% confidence interval)
	Outcomes in hospital		
	Skin breaks [b]	14	30 (between 18 and 49)
	Deep vein thrombosis that will cause symptoms and need treatment [b]	63	45 (between 34 and 62)
	Deep vein thrombosis that may or may not cause symptoms [c]	149	113 (between 94 and 136)
OHS *	**Outcomes at 6 months [b,d]**		
0-4	Alive and not severely disabled [e]	562	550 (between 517 and 590)
5	Alive but severely disabled	180	218 (between 187 and 252)
6	Dead [f]	258	232 (between 204 and 259)

[a] Absolute risk: number of cases per 1000 patients (95% confidence interval).

[b] Data from CLOTS-3 trial. [57,58]

		Standard best medical care (cases per 1000 patients)	Standard best medical care plus intermittent pneumatic compression (IPC) [a] (cases per 1000 patients, with 95% confidence interval)

[c] Data from Lacut (2005)[182] and CLOTS-3 trial.[57,58]

[d] These are average outcomes at 6 months after stroke, assessed using the Oxford Handicap Scale8. However, death rate and functional outcomes will vary depending on the severity of the initial stroke.

[e] The difference between the 2 groups on this outcome is not statistically significant.

[f] The difference between the 2 groups on this outcome is not statistically significant. However, when 6-month all-cause mortality data from the CLOTS-3 trial are pooled with 3-month data from the Lacut (2005) trial, the survival effect favouring IPC is statistically significant.

* The Oxford Handicap Scale is a categorical scale for measuring functional outcome after a stroke. Key: 0 = Healthy survival – fully independent; 1 = Minor symptoms – independent, no interference; 2 = Minor disability – independent, some restrictions but able to self-care; 3 = Moderate disability – significant restriction, unable to lead a totally independent existence (requires some assistance); 4 = Moderate-to-severe disability – unable to live independently but does not require constant attention; 5 = Severe disability – totally dependent, requires constant attention day and night; 6 = Death.

H.13 Acutely ill medical patients

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cohen et al., 2006 [61] Country of study: 35 centres in 8 countries	Patient group: Older acute medical patients Congestive heart failure (212/849) Acute respiratory distress (167/849) Acute infectious or inflammatory	Group 1 Fondaparinux (Atrixa) Start time: within 48 hours of admission End time: 1-13 days	All-cause mortality Follow up: 1 month	Group1: 14/425 Group 2: 25/414 P value: 0.071*	Funding: Sanofi-Synthelabo and NV Organon sponsored the study and carried out on-site monitoring of all
			Fatal pulmonary embolism (confirmed by: autopsy or no other explainable reason) Follow up: 1 month	Group1: 3/425 Group 2: 7/414 P value: 0.218*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: RCT List who was masked to interventions: Patient, clinician, outcome adjudicators Evidence level: 1+ Duration of follow-up: Asymptomatic events: 15 days Symptomatic events: 1 month	disease (214/849) Setting: Not stated Inclusion criteria: Patients aged ≥60 years and expected to remain in bed for at least 4 days and with acute illness: Congestive heart failure class III/IV, acute respiratory illness in the presence of chronic lung disease or clinically diagnosed acute infections or inflammatory disorders such as arthritis, connective tissue diseases, or inflammatory bowel disease. Exclusion criteria: High risk for bleeding, acute bacterial endocarditis, cerebral metastasis, recent haemorrhagic or ischaemic stroke, brain, spinal or ophthalmological surgery, an indwelling intrathecal or epidural catheter, a serum creatinine level >180 µmol/l in a well hydrated patient, documented hypersensitivity to contras media, anticipated intubation for more than 24 hours, use of anti-thrombotics within 48 hours before randomisation, an indication for anticoagulant prophylaxis or therapy, or life	(median 7 days) 2.5mg in 0.5ml saline subcutaneously once per day. Group 2 Placebo Start time: with 48 hours of admission End time: 1-15 days (median 7 days) 0.5 ml isotonic saline subcutaneously once per day. Additional non-comparative prophylaxis: Aspirin and NSAIDs discouraged. AES and physiotherapy were allowed (no information re: how many used	Symptomatic pulmonary embolism (confirmed by: high probability lung scan, pulmonary angiography or helical computed tomography) Follow up: 1 month	Group1: 4/425 Group 2: 11/414 P value0.212* (Includes fatal PE)	participants. The sponsors had an opportunity to comment on the manuscripts before submission. Fondaparinux is manufactured by GlaxoSmithKline Limitations: Diagnosis for fatal PE includes where death was sudden and where no other explainable reason was found. Relatively high number of patients for whom the primary outcome could not be evaluated (195/849) due to either
			Symptomatic DVT (confirmed by: bilateral venography) Follow up: 1 month	Group1: 0/429 Group 2: 0/420 P value: NS	
			DVT, asymptomatic or symptomatic (confirmed by venography) Follow up: 15 days	Group1: 18/321 Group 2: 29/323 P value: 0.129*	
			Thigh DVT (confirmed by: bilateral venography) Follow up: 15 days	Group1: 5/321 Group 2: 7/323 P value: 0.772*	
			Calf DVT (confirmed by: bilateral venography) Follow up: 15 days	Group1: 13/321 Group 2: 22/323 P value: 0.164*	
			Fatal bleeding Follow up: 1 month	Group1: 2/425 Group 2: 1/414 P value: 1.00*	
			Major bleeding (description: bleeding in a critical location, bleeding leading to surgical intervention, overt bleeding	Group1: 1/425 Group 2: 1/414 P value: 1.00*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	expectancy of less than one month. All patients N: 849 M/F: 360/489 Additional risk factors: Gp1 Gp2 Age ≥ 75 233 216 History of VTE 18 21 Cancer 62 69 Group 1 No. randomised: 429 No. of dropouts: 108 Mean Age (SD): 75.0 (8.3) Group 2 No. randomised: 420 No. of dropouts: 97 Mean Age (SD): 74.4 (8.3)	this)	associated with a drop in haemoglobin concentration of ≥20 g/l or leading to transfusion of 2 or more units of red blood cells.) Follow up: 15 days		no venography completed or venogram not evaluable. Outcomes not reported: LoS, QoL, pulmonary hypertension, post thrombotic syndrome, HIT, Neurological bleeding, upper GI bleeding. Additional outcomes reported: None. Notes: Many of the authors participators, consultants or both for NV Organon and Sanofi-Synthelabo 2 authors were employees of Organon. Outcomes reported
			Minor bleeding (description: Clinically relevant overt bleeding not meeting the criteria for major bleeding.) Follow up: 15 days	Group1: 11/424 Group 2: 4/414 P value: 0.116*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					from the number analysed not number randomised. * p values calculated by NCC-AC using Fisher Exact test

Study	Cohen 2013[63]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=8101)
Countries and setting	Conducted in Unknown multicentre; Setting: 556 sites in 52 countries
Line of therapy	Not applicable
Duration of study	Intervention time: Interventions - 10±4 days; Placebo for 35±4 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major bleeding - Bleeding leading to a ≥2 g/dl fall in haemoglobin or a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding into a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) or bleeding leading to death. Clinically relevant non-major bleeding - Overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, temporary cessation of study treatment or discomfort for the subject such as pain, or impairment of activities of daily life.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥40 years, Patients at risk of venous thromboembolic events hospitalized for the following acute medical conditions: Heart failure, NYHA class III or IV, active cancer (e.g. admitted for chemotherapy or for treatment of active cancer complication), acute ischemic stroke, acute infectious and inflammatory diseases, including acute rheumatic diseases, acute respiratory insufficiency; Patients with at least one additional risk factor for VTE: severe varicosis, chronic venous insufficiency, history of cancer, history of DVT/PE, history of heart failure (NYHA class III/IV), thrombophilia (hereditary or acquired), recent major surgery or serious trauma (6–12 weeks), hormone replacement

Study	Cohen 2013[63]
	therapy, advanced age ≥75 years, morbid obesity (body mass index ≥35 kg/m2), acute infectious disease contributing to hospitalization; Anticipated complete immobilization* for ≥1 day during the hospitalization and anticipated decreased level of mobility† for ≥4 days after randomization in any type of care setting and additional anticipated on-going decreased mobility thereafter, hospitalized <72 h before randomization.
Exclusion criteria	Contraindications for the use of the LMWH enoxaparin, bleeding risk-related criteria including: clinically significant bleeding, within 30 days of randomization, major surgery, biopsy of a parenchymal organ, ophthalmic surgery, or serious trauma within 6 weeks before randomization; Concomitant conditions or diseases e.g.: Known allergy to rivaroxaban or its excipients, severe renal insufficiency; Treatment with or use of mechanical thromboprophylaxis (e.g. pneumatic compression devices, foot pumps) for VTE); pregnancy
Recruitment/selection of patients	From December 2007 through July 2010, a total of 8428 patients were enrolled at 556 sites in 52 countries.
Age, gender and ethnicity	Age - Median (range): 71.0 years. Gender (M:F): 1.18/1. Ethnicity: 68.2% White; 19.9% Asian; 7.05% Other
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Rivaroxaban 28.2; Enoxaparin 28.2). 2. Mobility: Not stated 3. Renal impairment: Not stated
Extra comments	Acute medical condition (mean %): Infectious disease 45.5%; Heart failure 32.4%; Respiratory insufficiency 28%; Ischemic stroke 17.3%; Active cancer 7.3%; Inflammatory or rheumatic disease 3.8%; Other 0.7%; ≥ 2 medical conditions 31%. . History of heart failure: 34.5%; History of cancer: 17%; Acute ischemic stroke with leg paresis: 16.4%; Chronic venous insufficiency 14.8%; Severe varicosis: 11.9; History of DVT or PE: 4.7%; Hormone-replacement therapy: 1.2%; Major surgery within the previous 6 to 12 weeks: 0.8%; Hereditary or acquired thrombophilia: 0.3%; Serious trauma within the previous 6 to 12 weeks: 0.2%
Indirectness of population	No indirectness
Interventions	(n=4050) Intervention 1: Rivaroxaban. 10 mg once daily subcutaneous rivaroxaban for 35±4 days and subcutaneous placebo for 10±4 days. Duration Rivaroxaban 35±4 days; Placebo for 10±4 days . Concurrent medication/care: Ultrasonography was performed in all patients for the detection asymptomatic DVT after the last dose of study medication or matching placebo was administered on day 10±4 and on day 35±4 (n=4051) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin. 40 mg once daily, subcutaneous enoxaparin for 10±4 days. Oral placebo for 35±4 days. Duration Enoxaparin 10±4 days; Placebo 35±4 days . Concurrent medication/care: Ultrasonography was performed in all patients for the detection asymptomatic DVT after the last dose of study medication or matching placebo was administered on day 10±4 and on day 35±4.
Funding	Funding not stated

Study	Cohen 2013[63]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN versus ENOXAPARIN Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: Death from any cause at 35 days; Group 1: 159/3096, Group 2: 153/3169; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: VTE-related death at 35 days; Group 1: 19/2967, Group 2: 30/3057 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 35 days; Group 1: 116/2967, Group 2: 148/3057; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome: PE at 35 days ; Group 1: 10/2967, Group 2: 14/3057; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 35 days; Group 1: 43/3997, Group 2: 15/4001; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Venous thromboembolism at 7-90 days from hospital discharge (not analysed) - Actual outcome: Symptomatic VTE at 35 days; Group 1: 18/3997, Group 2: 12/4001	
Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Dahan et al., 1986 [74]	Patient group: Elderly medical patients (conditions: heart failure 49, respiratory diseases	Group I LMWH 10169 (renamed	All-cause mortality	Group 1: 6/135 Group 2: 6/135 P value: ns	Funding: not reported

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: France Study design: RCT List who was masked to interventions: patients Evidence level: 1+ Duration of follow-up: 10 days	57, ischemic stroke 46, malignant diseases 35, diabetes 12, depression 10, syncope 13, infection 11, neurologic diseases 7, joint diseases 7, hepatic or biliary diseases 4, miscellaneous 8). Setting: hospital Inclusion criteria: ■ age >65 Exclusion criteria: surgical patients on-going anticoagulant/platelet inhibitor therapy need for full anticoagulation presence of active bleeding presence of coagulation disorder predictable short-term hospitalisation (<7 days) All patients N: 270 No. of dropouts: 7 Risk Factors: Gp1 Gp2 Obesity (>10% ideal weight for age, sex and height) 13 12 Arrhythmia 23 29 Varicose veins 30 34	enoxaparin) 60mg in a volume of 0.3ml started on admission and continued for 10 days Group II placebo Additional non-comparative prophylaxis: None Non-steroidal anti-inflammatory drugs, aspirin or platelet inhibitor therapy forbidden.	DVT, asymptomatic or symptomatic (diagnosed by fibrinogen uptake test) Fatal pulmonary embolism (diagnosed by autopsy)	Group 1: 4/132 Group 2: 12/131 P value: 0.03 Group 1: 1/132 Group 2: 3/131 P value: ns	Limitations: Only patients appear to be masked to treatment. The study is over 20 years old, not reported if allocation to interventions was concealed from patients and participants Outcomes not reported: pulmonary embolism, proximal and distal DVT, major and minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life, length of stay

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Previous history of VTE 6 6 Immobilisation 43 42 Dehydration 28 38 Group I No. randomised: 135 No. of dropouts: 3 Age (mean): 79.9 +6.8 M/F: 84/51 Additional risk factors: Other factors: Group II No. randomised: 135 No. of dropouts: 4 Age (mean): 80.1 +6.9 M/F: 83/52 Additional risk factors: Other factors:				Additional outcomes reported: measurements for haemoglobin, platelets and activated partial anti-thrombin time Notes: Mean red cell count significantly lower in LMWH group (4.42 +0.63 106/mm3) compared to placebo

Study	Goldhaber 2011[123]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=6528)
Countries and setting	Conducted in Unknown multicentre; Setting: 302 centres in 35 countries
Line of therapy	Not applicable
Duration of study	Intervention time: Apixaban 30 days; Enoxaparin 6-14 days
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: DVT/PE: Detected with the use of systematic bilateral compression ultrasonography; Major bleeding: . Bleeding was categorized as major if it was fatal or overt and was accompanied by one or more of the following: a decrease in haemoglobin of 2 g or more per decilitre over a 24-hour period; transfusion of 2 or more units of packed red cells; or intracranial, intraspinal, intraocular, pericardial, or

Study	Goldhaber 2011[123]
	retroperitoneal bleeding, bleeding that occurred in an operated joint that required reoperation or intervention, or intramuscular bleeding with the compartment syndrome. Clinically relevant non-major bleeding was defined as acute, clinically overt bleeding that did not meet the criteria for classification as a major bleeding event but did meet at least one of the following criteria: epistaxis that required medical attention or persisted for 5 minutes or more, gastrointestinal bleeding containing frank blood or coffee-ground material that tested positive for blood, endoscopically confirmed bleeding, spontaneous haematuria or haematuria persisting for 24 hours or more after urinary-tract catheterization, unusual bruising, radiographically confirmed hematoma, or haemoptysis.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female patients, 40 years of age or older, were considered for participation in the study if they were hospitalized for congestive heart failure, acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease and had an expected hospital stay of at least 3 days.
Exclusion criteria	Patients with congestive heart failure or respiratory failure, eligible patients had to have at least one of the following additional risk factors: an age of 75 years or older, previous documented venous thromboembolism or a history of venous thromboembolism for which they received anticoagulation for at least 6 weeks, cancer, a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more, receipt of estrogenic hormone therapy, or chronic heart failure or respiratory failure.
Recruitment/selection of patients	From June 2007 through February 2011, acutely ill medical patients were enrolled at 302 centers in 35 countries
Age, gender and ethnicity	Age - Median (range): 67-68 years. Gender (M:F): 1/1.04. Ethnicity: White 76%, Black 9.2%; American Indian or Alaskan Native 0.2%, Asian 9.9%, Other 4.5%
Further population details	1. BMI : Obese (BMI over 30 kg/m2) (Apixaban 44.5%; Enoxaparin 44.3%). 2. Mobility: Mixed (Severely restricted: apixaban 26%, enoxaparin 28.4%; Moderately restricted: apixaban 73.4%, enoxaparin 71%). 3. Renal impairment: Not stated
Extra comments	Previous VTE: 4.1% ;History of cancer: 9.7%;Chronic heart failure: 47%; Chronic respiratory failure: 51.9%; Oestrogenic hormone therapy: 1.2%
Indirectness of population	No indirectness
Interventions	(n=3255) Intervention 1: Apixaban. Apixaban administered orally at a dose of 2.5 mg twice daily. Patients who were randomly assigned to apixaban received daily injections of an enoxaparin placebo for a minimum of 6 days. Duration 30 days. Concurrent medication/care: After 6 days, the decision to discontinue the parenteral study drug was made at the discretion of the investigators. Concomitant treatment with aspirin at doses above 165 mg per day was prohibited.

Study	Goldhaber 2011[123]
	(n=3273) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin. Enoxaparin, administered subcutaneously at a dose of 40 mg once daily during their stay in the hospital, for a minimum of 6 days. Duration 6 days. Concurrent medication/care: After 6 days, the decision to discontinue the parenteral study drug was made at the discretion of the investigators. Patients who were randomly assigned to enoxaparin received tablets containing an apixaban placebo for 30 days. Concomitant treatment with aspirin at doses above 165 mg per day was prohibited.
Funding	Study funded by industry (Bristol-Myers Squibb and Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN versus ENOXAPARIN Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: VTE-related death at 30 days; Group 1: 2/3255, Group 2: 3/3273; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge (data not analysed) - Actual outcome: Symptomatic proximal DVT at 60 days; Group 1: 5/3255, Group 2: 12/3273; - Actual outcome: Asymptomatic proximal DVT at 60 days; Group 1: 52/2206, Group 2: 48/2269; - Actual outcome: Symptomatic DVT at 60 days; Group 1: 5/3255, Group 2: 16/3273; Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome: Nonfatal pulmonary embolism at 60 days; Group 1: 7/3251, Group 2: 8/3266; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 30 days; Group 1: 15/3184, Group 2: 6/3217; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Clinically relevant non-major bleeding at up to 45 days from hospital discharge - Actual outcome: Major bleeding and clinically relevant non-major bleeding at 30 days; Group 1: 85/3184, Group 2: 67/3217; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Harenberg et al., 1996 [138] Country of study: Germany Study design: Multicentre double blind study List who was masked to interventions: Investigator and patients, critical event committee Evidence level: 1+ Duration of follow-up: 10 days	Patient group: Hospitalised, bed ridden patients with increased risk of thrombosis Setting: Inpatient, 10 centres in Germany Inclusion criteria: Aged 50-80 years Expected duration of bed rest >10 days ≥ 1 of the following risk factors present: obesity varicosis chronic venous insufficiency post thrombotic syndrome intake of oral contraceptives or oestrogen thrombocytosis >450,000/microL hyperviscosity syndrome previous myocardial infarction thrombotic cerebral infarction peripheral arterial ischaemic Exclusion criteria: known intolerance to heparin thrombocytopenia <80m000micro/L hereditary or acquired coagulation disorder acute DVT pre-treatment with heparin other than study medication	Group 1 UFH 5000IU , 3 times daily, subcutaneously, at 8 hour intervals Group 2 Fraxiparine 36mg (3100IU of antiXa), plus 2 placebo injections, 3 times daily, at 8 hour intervals Start time: within 12 hours of admission to hospital End time: day 11 Duration: 10 days Additional non-comparative prophylaxis: (list or write not reported or not applicable)	All-cause mortality	Group1: 9/780 Group 2: 23/810 P value: 0.02 In group1, causes of death were carcinoma (4), pneumonia (1), chronic obstructive pulmonary disease (1), cardiac insufficiency (1), atrial fibrillation (1) and renal insufficiency (1) respectively. In Group 2 causes of death were carcinoma (3), pneumonia (4), stroke (4), cardiac insufficiency (9), myocardial infarction (1) and PE (1) and diabetes (1) respectively.	Funding: Not stated Limitations: Reporting focused on safety outcomes (blood test results), DVT and PE reporting not clear Incidences of death and primary endpoints were not equally distributed between centres. In centres where no primary end points were observed, incidence of death the in LMWH group was 3.5x higher Outcomes not reported: PE asymptomatic or symptomatic DVT, asymptomatic or symptomatic, Thigh DVT, Calf DVT Fatal bleeding Neurological bleeding Upper GI bleeding Heparin induced
			Fatal pulmonary embolism (confirmed by: perfusion scintigraphy, additional angiography or ventilation scintiscan performed if results were low probability defects)	Definite PE Group1: 0/780 Group 2: 1/810 P value: Probable PE Group1: 3/780 Group 2: 3/810 P value: 16 patients‟ death was classified as “possible” PE, but it was not stated which group they belonged to.	
			Symptomatic pulmonary embolism (confirmed by: perfusion scintigraphy, additional angiography or ventilation scintiscan performed if results were low probability defects))	Probable PE Group1: 3/780 Group 2: 3/810 P value:	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	regular intake of medication influencing blood coagulation unfavourable short term prognosis septicaemia with gram negative bacteria disseminated intravascular coagulation fixed hypertension history of any bleeding creatinine >3mg/dl prothrombin time <60% The post-operative phase is not an exclusion criteria All patients N: 1968 randomised, 378 excluded from efficacy analysis Main Diagnosis Gp1 Gp2 Cardiac insufficiency 143 150 Cerebrovascular diseases 134 149 Coronary heart disease 131 139 Cancer 63 57 Diabetes57 47 Gastro. Or neph. Disease 45 38 Chronic obstructive lung disease 46 41 Pneumonia or infections 16 26 Other diseases 144 166 Group 1		DVT, asymptomatic or symptomatic Or Symptomatic DVT?? (screening at Day 1 and Day 11 and upon presentation of clinical signs)	Group1: 1/780 Group 2: 3/ 810 P value: Not described whether symptomatic or asymptomatic. Likely to be all symptomatic cases, as none of them occurred on the day of planned scans.	thrombocytopaenia PTS, Pulmonary hypertension, QoL, LOS Additional outcomes reported: 4 cases of thrombocytopenia in UFH group, 0 in fraxiparine. Various clinical chemistry results Notes: DVT and PE events were combined and reported as “primary end points”. Study was designed as an equivalence study. Emphasis of report was on “safety”-clinical chemistry.
			Major bleeding no description of criteria Minor bleeding no description of criteria	Group1: 4/780 Group 2: 5/ 810 Group1: 7/ 780 Group 2: 3/810 P value: 0.34	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 985 No. of dropouts: 205(140 dropped out, 65 not eligible) Age (mean): 70.4±7.9 M/F: 372/408 Additional risk factors: -Smoker (no/ex/yes): 482/185/113 -Adiposity: 250 -Previous DVT:33 -Previous PE: 13 -*Varicosis: 137 -Ulcus cruris: 35 -Thrombocytosis: 33 -Peripheral AD: 160 -Previous MI: 113 -Previous stroke: 121 -Cardiac insufficiency: 343 -Hyperviscosity: 118 -Estrogen: 2 Group 2 No. randomised: 983 No. of dropouts: 173 (119 dropped out, 54 not eligible) Age (mean): 70.5±8.3 M/F: 344/466 Additional risk factors: -Smoker (no/ex/yes): 504/173/103 -Adiposity: 254				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	-Previous DVT: 50 -Previous PE: 18 -*Varicosis: 179 -Ulcus cruris: 33 -Thrombocytosis: 38 -Peripheral AD: 167 -Previous MI: 123 -Previous stroke: 119 -Cardiac insufficiency: 348 -Hyperviscosity: 112 -Estrogen: 4 *p=0.02				

Study	Hull 2010[153]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=5963)
Countries and setting	Conducted in Multiple countries; Setting: 370 hospitals across 20 countries
Line of therapy	Not applicable
Duration of study	Intervention time: Enoxaparin for 10± 4 days, Placebo 28±4 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was diagnosed using bilateral compression ultrasonography or venography, PE was diagnosed using computed tomography or ventilation–perfusion lung scanning.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible if they were at least 40 years of age, had a life expectancy of at least 6 months, and had recently reduced mobility for up to 3 days. In addition, they had to be considered by the enrolling investigator as likely to have reduced mobility for at least 3 days after enrolment. We defined “reduced mobility” as requiring total bed rest or being sedentary without bathroom privileges (level 1 immobility) or with bathroom privileges (level 2 immobility).

Study	Hull 2010[153]
Exclusion criteria	Not reported
Recruitment/selection of patients	Patients enrolled from 370 hospitals across 20 countries between February 2002 and March 2006
Age, gender and ethnicity	Age - Mean (SD): 67.9 (12.1) years. Gender (M:F): 1/1. Ethnicity: 74.8% White, 6.8% Black, 13.6% Hispanic, Asian or Oriental 2.7%; Multiracial 1.5%, Other 0.5%
Further population details	1. BMI : Obese (BMI over 30 kg/m2) (34% of population had BMI ≥ 30 kg/m2). 2. Mobility: Mixed (Level 1 immobility (total bed or sedentary without bathroom privileges) 43.2%; Level 2 immobility (total bed rest or sedentary with bathroom privileges) 56.5%). 3. Renal impairment: Not stated
Extra comments	Primary enrolment diagnoses (%): Acute infection without septic shock 33.2%; Acute respiratory insufficiency 30.3%; Heart failure 18.7%; Post-acute ischemic stroke 6.6%; Acute rheumatic disorders 2.7%; Active cancer 1.6%; Fracture 0.7%; Multiple diagnoses 0.6%; Active inflammatory bowel disease 0.3%; Other 5.7%. Age >75 years - 29.9%; Active or previous cancer - 13.7%; History of VTE - 6.8%; Venous insufficiency - 13.7%; Hormone therapy - 2.2%; Chronic heart failure - 25.6%; Chronic respiratory failure - 39.9%; Chronic inflammatory disease - 0.5%; Family history of VTE - 0.1%; Thrombophilia - 0.1%
Indirectness of population	No indirectness
Interventions	(n=2975) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin. Subcutaneous enoxaparin, 40 mg/d, for 10 ± 4 days, then further course of enoxaparin. Duration 28 ± 4 days. Concurrent medication/care: Some patients completed prophylaxis in outpatient setting (n=2988) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin. Received enoxaparin for 10 ± 4 days then placebo for an additional 28 ± 4 days. Duration 28 ± 4 days. Concurrent medication/care: N/A
Funding	Study funded by industry (Sanofi-aventis)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (EXTENDED DURATION) versus ENOXAPARIN (STANDARD)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 90 days; Group 1: 105/2176, Group 2: 105/2159; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge (not analysed)
- Actual outcome: Proximal DVT (symptomatic and asymptomatic) at 90 days; Group 1: 76/1867, Group 2: 45/1818

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge

Study	Hull 2010[153]
- Actual outcome: PE at 90 days; Group 1: 7/1867, Group 2: 3/1818; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Fatal PE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 90 days; Group 1: 2/1867, Group 2: 0/1818; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Venous thromboembolism at 7-90 days from hospital discharge (not analysed) - Actual outcome: VTE at 90 days; Group 1: 83/1867, Group 2: 48/1818 **Subgroup analysis evaluating patients with ischemic stroke: Turpie 2013[320]** RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus PLACEBO Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: 30-day mortality at 30d from start of trial of extension; Group 1: 5/198, Group 2: 8/191; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: 90-day mortality at 90d from start of trial of extension; Group 1: 8/198, Group 2: 11/191; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at During 28 day blind period (after open label treatment) plus seven days; Group 1: 4/165, Group 2: 11/150; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleed (Hb decrease at least 2g/dl) at During time of trial extension, plus two day after (30d total); Group 1: 3/198, Group 2: 0/191; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at During 28 day blind period (after open label treatment) plus seven days; Group 1: 0/166, Group 2: 1/150; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: DVT (symptomatic) - Actual outcome: Symptomatic DVT at During 28 day blind period (after open label treatment) plus seven days; Group 1: 0/166, Group 2: 2/150; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Hull 2010[153]
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge; Pulmonary embolism at 7-90 days from hospital discharge; Major bleeding at up to 45 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	Ishi 2013[156]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=92)
Countries and setting	Conducted in India; Setting: Intermediary care hospital in south India
Line of therapy	Not applicable
Duration of study	Unclear
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: No definitions reported
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Medically ill patients with high and higher risk of DVT/PE (as per the DVT/PE assessment score) in patients who required (1) at least 3 days of ICU stay or (2) same duration non-ambulatory condition in the wards among patients who were admitted to an intermediary care hospital.
Exclusion criteria	Moderate risk patients were not included in the study
Recruitment/selection of patients	March 2008 and July 2009
Age, gender and ethnicity	Age - Mean (range): 50.9-57.9 years. Gender (M:F): 2.4/1. Ethnicity: Not reported
Further population details	1. BMI: Not stated 2. Mobility: Not stated 3. Renal impairment: Not stated
Extra comments	Diagnosis: Stroke 19.9%, cardiological dysfunction 4.8%, sepsis 11.7%, toxicological causes 26.3%, multisystem disorder 13%, others 15.2% No. of days patients received prophylaxis: 3-5 days 23.1%, 6-10 days 59.3%, > 10 days 35.1%
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin. Enoxaparin 40 mg subcutaneously

Study	Ishi 2013[156]
	once daily. Thromboprophylaxis was continued until patient became ambulant and ready for discharge. Duration Unclear. Concurrent medication/care: NA (n=48) Intervention 2: Unfractionated heparin - low dose, administered subcutaneously. Unfractionated heparin - 5000 IU subcutaneously twice daily. Thromboprophylaxis was continued until patient became ambulant and ready for discharge. Duration Unclear. Concurrent medication/care: NA
Funding	Study funded by industry (Partly funded by Sanofi-Aventis Pharma the manufacturers of Clexane (Enoxaparin))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN versus UFH Protocol outcome 1: Venous thromboembolism at 7-90 days from hospital discharge (not analysed) - Actual outcome: DVT/PE (VTE) at Unclear; Group 1: 2/44, Group 2: 1/48 Protocol outcome 2: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Unclear; Group 1: 0/44, Group 2: 4/48; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Heparin-induced thrombocytopenia at up to 90 days from hospital discharge - Actual outcome: Heparin induced thrombocytopenia at Unclear; Group 1: 0/44, Group 2: 2/48; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge; Pulmonary embolism at 7-90 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	Kakkar 2011[163]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=8323)
Countries and setting	Conducted in China, India, Malaysia, Mexico, Philippines, South Korea, Tunisia; Setting: 193 sites in China, India, Korea, Malaysia, Mexico, the Philippines, and Tunisia

Study	Kakkar 2011[163]
Line of therapy	Not applicable
Duration of study	Intervention time: 6-14 days during hospitalisation
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A major haemorrhage was defined as overt bleeding associated with one of the following: death; the need for transfusion of at least 2 units of packed red cells or whole blood; a fall in the haemoglobin level of 20 g or more per litre; the requirement for a major therapeutic intervention (e.g., surgery) to stop or control bleeding; or a bleeding site that was retroperitoneal, intracranial, or intraocular. Clinically relevant non-major bleeding was defined as a non-major haemorrhage leading to discontinuation of the study drug or to hospitalization.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	enrolled men and women, 40 years of age or older, who were hospitalized within 48 hours before randomization for at least one of the following conditions: acute decompensation of heart failure; active cancer (defined as histologically confirmed cancer with an initial diagnosis within the previous 6 months or with a recurrence or metastasis within the previous 6 months), unless the hospitalization was a planned hospitalization for chemotherapy; or severe systemic infection in addition to at least one of the following conditions: chronic pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary fibrosis, or the pulmonary restrictive syndrome), obesity (a body-mass index [the weight in kilograms divided by the square of the height in meters] ≥30), a personal history of venous thromboembolism, or an age of 60 years or older. In addition, eligible patients were required to have an anticipated duration of hospitalization of at least 6 days and an American Society of Anesthesiologists health status score of 3 or less (on a scale of 1 to 6, with higher scores indicating more severe illness) or, for patients with cancer, an Eastern Cooperative Oncology Group performance status score of 2 or less (on a scale of 0 to 5, with higher scores indicating greater severity of illness).
Exclusion criteria	Major surgery or major trauma within the previous 6 weeks, need for ventilator support with intubation, symptomatic VTE at enrolment, multiple organ failure, evidence of an active bleeding disorder, contraindication to anticoagulation, cerebrovascular accident at inclusion or within 10 days prior to inclusion, prosthetic heart valves, confirmed cerebral metastases, known hypersensitivity to unfractionated heparin (UFH) or LMWH or pork-derived products, history of documented heparin-induced thrombocytopenia (HIT), participation in another clinical trial within the previous 30 days (patients with cancer included in a cancer-treatment protocol are allowed to participate only in cases where local regulations permit this and they are in the follow-up period of the cancer study and not scheduled to receive investigational cancer treatments during LIFENOX treatment/hospitalization period), persistent severe renal failure (creatinine clearance <30 mL/min on at least two occasions ≥3days before entry into the study), known or suspected severe anaemia or lumbar puncture within the preceding 24 hours, spinal or epidural analgesia with the preceding 24 hours, patients unlikely to be compliant, women of childbearing potential not protected by an effective method of

Study	Kakkar 2011[163]
	birth control, refusal or inability to give informed consent to participate in the study, and inability to be followed-up after hospital discharge until day 90 after randomization.
Recruitment/selection of patients	Recruitment began in January 2008 and was completed in September 2010.
Age, gender and ethnicity	Age - Mean (range): 65.3-65.6 years. Gender (M:F): 1.7/1. Ethnicity: Not reported
Further population details	1. BMI : Obese (BMI over 30 kg/m2) (10.5% in both the intervention and control arms). 2. Mobility: Not stated 3. Renal impairment: Renal impairment (eGFR less than 30 ml/min/1.73m2) (Intervention (Intervention group 35.5%; Placebo group 35.8%).
Extra comments	Primary reason for hospitalisation: Heart failure 31%; Severe systemic infection 57%; Active cancer 4.4%; Heart failure and severe systemic infection 6.2%; Heart failure and active cancer 0.2%; Severe systemic infection and active cancer 1.3%; Heart failure, severe systemic infection and active cancer 0.1%; None of the above 0.6%.
Indirectness of population	No indirectness
Interventions	(n=4174) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin. Subcutaneous injection with enoxaparin, at a dose of 40 mg (Lovenox [United States] or Clexane [outside the United States], Sanofi), once every 24±4 hours during hospitalisation. Duration 10±4 days. Concurrent medication/care: Knee-high AES (Ganzoni) that provided graduated pressure from 15 mm Hg (at the ankle) to 10 mm Hg (at the knee) were provided to both groups. (n=4145) Intervention 2: No treatment - Placebo. Patients were randomly assigned to receive a subcutaneous injection with placebo (0.9% saline),once every 24±4 hours during hospitalisation. Duration 10±4 days. Concurrent medication/care: Knee-high AES (Ganzoni) that provided graduated pressure from 15 mm Hg (at the ankle) to 10 mm Hg (at the knee) were provided to both groups.
Funding	Study funded by industry (Supported by Sanofi)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 90 days; Group 1: 348/4171, Group 2: 355/4136; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 8 days; Group 1: 16/4174, Group 2: 11/4145; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Clinically relevant non-major bleeding at up to 45 days from hospital discharge

Study	Kakkar 2011[163]
- Actual outcome: Clinically relevant non-major bleeding at 8 days; Group 1: 18/4174, Group 2: 14/4145; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge; Pulmonary embolism at 7-90 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kleber et al., 2003 (The PRINCE study) [172] Country of study: Germany Study design: Multicentre RCT, open label study List who was masked to interventions: Open label study. Central reviewers of efficacy end points (interpreting	Patient group: Heart failure (n=333)and respiratory disease(n=332) patients Setting: inpatient Inclusion criteria: Aged ≥18 Hospitalised for severe respiratory disease (based on lung function test or blood gas analyses outside normal range and at ≥1 of these: severe functional loss ≥2 lung segments, severe secondary pulmonary hypertension, pneumonia, interstitial lung disease, lung cancer and/or metastases with life expectancy > 2 months, or exacerbation of COPD)or heart failure (class III or IV according to New York Heart Association classification) Confined to bed >2/3 of the time Exclusion criteria:	Group 1 UFH 5000IU 3 times daily, subcutaneously Group 2 Enoxaparin 40mg once daily, subcutaneously Start time: Day 1(on enrolment day) Duration: 10±2 days Additional non-comparative prophylaxis: Patients on anticoagulants or platelet inhibitors, or	All-cause mortality (confirmed by:)	Group1: 15/333 Group 2: 9/ 332 P value:	Funding: Aventis Pharma Limitations: Open label study More patients with malignancy in the enoxaparin group Outcomes not reported: Symptomatic DVT Calf DVT Fatal bleeding Neurological bleeding Upper GI bleeding Heparin induced thrombocytopaenia PTS, Pulmonary hypertension QoL, LOS
			Fatal pulmonary embolism (confirmed by: Autopsy. 1 heart failure patient in UFH group had both PE and DVT)	Group1: 1/212 Group 2: 0/239 P value:	
			Symptomatic pulmonary embolism (confirmed by: perfusion scintigram)	Group1: 0/212 Group 2: 1/239 P value:	
			DVT, asymptomatic or symptomatic (confirmed by: patients with positive D dimmer or fibrin monomer test underwent bilateral venography. Autopsy) 1 heart failure patient in UFH group had both PE and DVT	By D-dimer test Group1: 86/212 Group 2: 84/236 P value: By Venography/autopsy, including venogram conducted >24 hours after last dose Group1: 28/235 Group 2: 26/264 P value:	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
the screening tests and assessment of venous thromboembolic events) were masked. Evidence level: 1+ Duration of follow-up: 10±2 days	Advanced acquired immunodeficiency syndrome Contraindication to LMWH or UFH Hypersensitivity to contrast media Severe hepatic, pancreatic or renal disease, arterial hypertension Intracranial bleeding or haemorrhagic stroke in the preceding 6 months Ocular ocr CNS surgery in the preceding 4 weeks Coagulation disorders Drug/alcohol abuse Acute signs of DVT or PE Gastrointestinal ulcer Immobilised for > 24 hours before enrolment Patients on anticoagulants or platelet inhibitors, or NSAIDs. However, heart failure patients allowed 100mg aspirin All patients No randomised: 668 (3 withdrawn before receiving any study medication) No. of dropouts: 214/665 Age (mean): 70±14 Risk Factors Gp1 Gp2 Immobilisation 332 333 Congestive heart failure 186 186 Age >70yr 185 187	NSAIDs. However, heart failure patients allowed 100mg aspirin AES applied up to 20% of patients in each treatment group		By Venography/autopsy, in primary efficacy population Group1: 22/212 Group 2: 19/239 P value: In heart failure patients: By Venography/autopsy Group1: 15/93 Group 2: 11/113 P value: In respiratory failure patients By Venography/autopsy Group1: 7/119 Group 2: 8/126 P value	Additional outcomes reported: Notes:
			Thigh (Proximal)DVT(confirmed by:)	Group1: 4/ 212 Group 2: 9/ 239 P value:	
			Major bleeding (description: 1 urogenital –enoxaparin and 1 haemorrhoidal-UFH. Defined as retroperitoneal or intracranial bleeding, overt bleeding with Hb)	Group1: 1/333 Group 2: 1/332 P value:	
			Minor bleeding (description:)	Group1: 11/333 Group 2: 4/332 P value:	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	COPD 134 142 Venous Disease 137 129 Overweight 104 98 Diabetes Mellitus 101 104 Severe infection 61 56 Pervious myocardial infarction 41 41 Pre-existing malignancy 25 16 Dehydration 15 23 History of DVT 20 19 Group 1 No. randomised: 333 M/F:183/150 No evaluated: 212 Severe respiratory disease:164 Heart failure:169 Group 2 No. randomised: 332 M/F:160/172 No evaluated: 239 Severe respiratory disease:168 Heart failure:164				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lechler et al., 1996 [199] Country of	Patient group: Immobilised medical patients	Group 1 UFH 5000IU 3 times daily, subcutaneously	All-cause mortality (confirmed by:)	Group1: 11/482 Group 2: 7/477 P value: 0.47 [calculated by NCCAC team using	Funding: Limitations:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
study: Austria and Germany Study design: RCT, double blinded, multi centre List who was masked to interventions: Patients and investigators Evidence level: 1+ Duration of follow-up: 7 days	Setting: 26 medical centres Inclusion criteria: ≥18 years old expected immobilisation of >1/2 of the time for the whole study period of 7 days, and at least one of additional risk factors such as: age >60 years malignancy obesity (>20%) former thromboembolic event cardiac insufficiency (NYHA III-IV) paresis of lower limbs hemiplegia/paraplegia severe infection Exclusion criteria: Anticoagulation and/or treatment with aggregation inhibitors or NSAIDS for the preceding 7 days Regional anaesthesia Pregnancy or lactation Bleeding disorder Thrombocytopenia (<100,000/µL) Head trauma in the past 6 months Haemorrhagic stroke in the preceding 4 weeks Endocarditis Suspicion for internal bleeding Severe liver disease/renal insufficiency	Group 2 Enoxaparin 40mg, daily and 2 placebo injection(isotonic mannitol solution) (total of 3 injections daily) All injections were 0.2 ml Start time: within 24 hours of admission Duration: 7 days Additional non-comparative prophylaxis: Patients on anticoagulants, aggregation inhibitors and NSAIDs were excluded from study Mechanical prophylaxis unknown		Fisher's exact test]	Not reported: o Method of randomisation/ concealment o Results across centres o Mortality causes o Mechanical prophylactic methods, or ambulation policies Outcomes not reported: Fatal PE, Symptomatic PE, Symptomatic DVT, Major bleeding, Minor bleeding, Heparin induced thrombocytopaenia PTS, Pulmonary hypertension, QoL, LOS Additional outcomes reported: 8 urogenital bleedings reported-not stated which group.
			Symptomatic pulmonary embolism (confirmed by: perfusion scan, angiography and autopsy in cases of death if permitted)	Group1: 4/443 Group 2: 0/442 P value: 0.12 [calculated by NCCAC team using Fisher's exact test]	
			DVT, asymptomatic or symptomatic (confirmed by: duplex sonography at end of study period, or when clinically suspected. Positive cases were confirmed with phlebography)	Group1: 4/443 Group 2: 1/442 P value: 0.38 [calculated by NCCAC team using Fisher's exact test]	
			Major bleeding (description: decrease in Hb≥2g/dl, transfusion of >2 units of blood and/or retroperitoneal or intracranial bleeding)	Group1: 7/482 Group 2: 2/477 P value: 0.18 [calculated by NCCAC team using Fisher's exact test] 2 patients in heparin group were reported to have "severe bleeding". However, the definition was not provided.	
			Upper GI bleeding	9 gastrointestinal bleeding cases. Not stated which group it was from.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Thromboembolism on admission and participation in a clinical trial in the preceding 6 weeks All patients N: 959 Age (mean): 74±13 Main Diagnoses (%): Gp1 Gp2 Cardiovascular diseases 67.5 70.5 Endocrinologic diseases 27.9 30.1 Respiratory diseases 24.3 23.4 Gastrointestinal and urogenital diseases 22.6 21.8 Central nervous diseases 15.8 17.8 Cancer 14.7 12.9 Bone diseases 10.8 12.2 Skin diseases 3.5 3.1 Others 8.2 8.9 Group 1 No. randomised: 482 Stipulated efficacy evaluation conducted: 443 Per protocol population:377 M/F: 178/304 Age (mean): 74±13 Risk factors (%) -Immobilisation: 100 -Age >60 years: 88.8 -Heart failure: 35.9				Haematomas >5 cm in diameter: 52 events in UFH and 22 in enoxaparin Notes: All patients were screened for DVT at study entry using B- mode scan or duplex sonography.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	-Overweight: 32.8 -Severe infection: 19.1 -Malignant disease: 14.7 -Paresis hemiplegia, paraplegia: 7.5 -Previous VTE: 7.7 Group 2 No. randomised: 477 Stipulated efficacy evaluation conducted: 442 Per protocol population:393 M/F: 183/294 Age (mean): 74±13 Risk factors (%) -Immobilisation: 100 -Age >60 years: 87.2 -Heart failure: 34.2 -Overweight: 28.7 -Severe infection: 20.1 -Malignant disease: 20.1 -Paresis hemiplegia, paraplegia: 7.5 -Previous VTE: 6.1				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lederle et al., 2006 [202] Country of	Patient group: Hospitalised general medical patients age 60 or over	LMWH Enoxaparin 40 mg syringes. Subcutaneous	All-cause mortality at 90 days	Enoxaparin: 13/140 Placebo: 14/140 P value: Not reported. RR (95% CI): 0.93 (0.26-1.59)	Funding: Supported by the Cooperative Studies Program of the

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
study: US Study design: RCT List who was masked to interventions: Double blind: patient, clinician and researcher Evidence level: 1+ Duration of follow-up: 90 days (although number of deaths at 1 year is reported)	Setting: Medical ward, intensive care units or intermediate care Inclusion criteria: Admitted or transferred (from home or another hospital, institution, or service) to the medical service (medical wards or intensive care units or intermediate care) of the participating Veterans Affairs medical centre on the day of randomisation or the previous day. Age 60 years or older expected to be at the medical centre for at least 3 days from the time of randomisation able and willing to give informed consent. Exclusion criteria: ■ Already receiving or requiring anticoagulation for reasons other than VTE prophylaxis ■ known thrombocytopenia (platelet count < 100000/mm3) systolic blood pressure higher than 220 mm Hg diastolic blood pressure higher than 110 mm Hg ■ other contraindication to low-dose heparin in the opinion of the patient's physicians previous randomisation into the study,	daily injections. First injection given immediately after randomisation. Placebo Group Identical syringes containing placebo. Treatment was withheld if the patient developed any of the following: need for anticoagulation or thrombolytic therapy, decrease in platelet count of 50%, systolic pressure higher than 220 mm Hg or diastolic pressure more than 110 mm Hg, other contraindication to low- dose heparin in the opinion of the attending physicians, change of status to	All-cause mortality at 1 year	Enoxaparin: 36/140 Placebo: 32/140 P value: Not reported. RR (95% CI): 1.13 (0.66-1.60)	Department of Veterans Affairs Office of Research and Development. Enoxaparin and matching placebo syringes were provided by Rhone-Poulene Rorer Pharmaceuticals. Limitations: Very small sample size. This pilot study aimed to recruit 1000 patients and only 280 patients (140 in each group) were recruited. The pilot study was not large enough to answer the study question. 32 (23%) patients in enoxaparin group
			Symptomatic pulmonary embolism at 90 days (ventilation perfusion scan, pulmonary angiogram or autopsy)	Reported as "Pulmonary embolism" in table Enoxaparin Group: 1/140 Placebo Group: 3/140 P value: Not reported. Difference was NS	
			Major bleeding (description: No details provided)	Enoxaparin Group: 2/140 Placebo Group: 5/140 P value: Not reported. Difference was NS	
			Heparin induced thrombocytopaenia	Enoxaparin Group: 1/140 Placebo Group: 3/140 P value: Not reported. Difference was NS	
			Length of stay (mean total hospital days, initial and readmissions)	Enoxaparin Group: 13.4 Placebo Group: 11.1 P value: Not reported. Difference was NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	"supportive/palliative care only" status occurrence within the past 30 days of myocardial infarction, stroke, major surgery (defined as requiring general, spinal, or epidural anaesthesia and lasting >30 minutes), or any eye surgery. All patients N: 280 Enoxaparin Group No. randomised: 140 No. of dropouts: 2 Age (mean): 71.3 M/F: 99.3 % men Additional risk factors: Weight (kg): 85.1 (units not reported) White race: 83.2 % Current pneumonia: 15 % Current smoker: 17.9 % History of: Thromboembolism: 5.7 % Heparin: 9.3 % Cancer: 5.0 % Cerebrovascular disease 8.6% Chronic obstructive lung disease 47.1 % Diabetes: 27.9 %	supportive/palliative care only, of if more than 90 days had elapsed since randomisation. Additional non-comparative prophylaxis: Not reported			and 25 (18%) in the placebo group had study drug discontinued. Outcomes not reported: fatal pulmonary embolism; thigh & calf DVT; fatal, neurological, upper GI or minor bleeding; post thrombotic syndrome; pulmonary hypertension; quality of life Additional outcomes reported: stroke, myocardial infarction, no. patients readmitted, DVT but not clear how diagnosed

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Congestive Heart Failure: 22.1 % Myocardial infarction: 25.7 % Peripheral vascular disease: 22.0 Surgery in the past 6 months: 2.9 % Charlson Comorbidity Index (score): 2.49 % Self-reported general health: Excellent: 2.3% Good: 16.2 % Fair: 68.5% Poor: 13.1 % Placebo Group No. randomised: 140 No. of dropouts: 1 Age (mean): 72.1 M/F: 97.8% men Additional risk factors: Weight (kg): 85.5 (units not reported) White race: 75.2 % Current pneumonia: 19.3 % Current smoker: 15.0 % History of: Thromboembolism: 3.6 % Heparin: 8.6 % Cancer: 4.3 % Cerebrovascular disease 11.4% Chronic obstructive lung disease 40.0 % Diabetes: 28.6 %				Notes: Authors do not provide detailed information on how outcomes were measured. Causes of deaths and drug discontinuation are not described.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Congestive Heart Failure: 27.1 % Myocardial infarction: 22.9 % Peripheral vascular disease: 10.0 p= 0.02 Surgery in the past 6 months: 2.9 % Charlson Comorbidity Index (score): 2.47 % Self-reported general health: Excellent: 3.0% Good: 21.1 % Fair: 56.4% Poor: 19.5 %				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Leizorovicz et al., 2004 [203] Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE (The PREVENT Study) Country of study: Multi-national	Patient group: -Acutely ill medical patients with one of: acute congestive heart failure acute respiratory failure not requiring mechanical ventilation Or one of following with >1 risk factors listed in last point: acute infection without septic shock episode of inflammatory bowel disease acute rheumatic disorders acute lumbar pain, sciatica or vertebral compression acute arthritis of the legs or acute	Group I LMWH dalteparin 5000 IU 1x/day for 14 days Group II placebo 1x/day for 14 days Additional non-comparative prophylaxis: Low dose aspirin (up to	All-cause mortality at day 14	Group 1: 8/1846 Group 2: 7/1831 Relative risk: 1.13 (0.41, 3.12)	Funding: Pharmacia Limitations: Not clear if clinicians treating patients were masked to treatment, not reported if allocation to interventions was concealed from patients
			All-cause mortality at day 21	Group 1: 43/1829 Group 2: 42/1807 Relative risk: 1.01 (0.66, 1.54)	
			All-cause mortality at 90 days	Group 1: 107/1747 Group 2: 103/1715 Relative risk: 1.02 (0.78, 1.33)	
			Fatal pulmonary embolism at day 21 (confirmed by autopsy)	Group 1: 0/1829 Group 2: 2/1807 Relative risk: 0.00	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: RCT List who was masked to interventions: Subjects and investigators of VTE assessment Evidence level: 1+ Duration of follow-up: 14 days treatment, 90 days follow-up	episode of rheumatoid arthritis in the legs risk factors: age >75, cancer, previous VTE, obesity, varicose veins, chronic venous insufficiency, hormone therapy, chronic heart or respiratory failure or myeloproliferative disorder Setting: hospital Inclusion criteria: -immobilised but have been for <3 days -projected hospital stay of >4 days ->40 years old Exclusion criteria: -acute coronary syndrome within previous month -major surgical or invasive procedure within previous month or to be undertaken within next 2 weeks - bacterial endocarditis -immobilised lower limb due to cast or fracture -stroke within previous 3 months -high risk of bleeding	325mg/day), ticlopidine and clopidogrel permitted; "Chronic use" non- steroidal anti-inflammatory drugs discourage but not forbidden. Other antithrombotic agents not permitted, anyone given one of these withdrawn from the study Numbers not given for any of the above	Symptomatic pulmonary embolism at day 21 *	Group 1: 5/1759 Group 2: 4/1740 Relative risk: 1.22	and participants Outcomes not reported: post-thrombotic syndrome, quality of life, length of stay Additional outcomes reported: thrombocytopenia (not stated if heparin induced thrombocytopenia), Notes: * pulmonary embolism diagnosed by ventilation-perfusion scanning, pulmonary
			Symptomatic pulmonary embolism at day 90 *	Group 1: 5/1615 Group 2: 6/1583 Relative risk: 0.82 (0.25, 2.67)	
			Symptomatic distal DVT at day 21 $	Group 1: 3/1759 Group 2: 4/1739 Relative risk: 1.22	
			Symptomatic proximal DVT at day 21 $	Group 1: 2/1759 Group 2: 7/1739 Relative risk: 0.28 ()	
			Asymptomatic proximal DVT at day 21 $	Group 1: 27/1507 Group 2: 53/1453 Relative risk: 0.48 (0.31, 0.77)	
			DVT: any proximal and symptomatic distal at day 21	Group 1: 32/1508 Group 2: 64/1464 Relative risk: 0.49 (0.32, 0.74)	
			Symptomatic VTE at 90 days	Group 1: 15/1615 Group 2: 21/1583 Relative risk: 0.70 (0.36, 1.35)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	-platelet count <100x109/L -heparin or LMWH given for >48 hours before randomisation -contraindication to heparin anticoagulation -creatinine >2.0mg/dL -hepatic insufficiency or active hepatitis -pregnancy or breast feeding -life expectance <1 month All patients N: 3706 No. of dropouts: 25 Primary Diagnosis Gp1 Gp2 Acute congestive heart failure (NYHA class III or IV) 965 940 Acute respiratory failure 561 560 Infectious disease 673 687 Rheumatological disease 200 198 Inflammatory bowel disease 10 8 Group I No. randomised: 1848		All symptomatic DVT at 90 days Major bleeding at day 21 £ Major bleeding at day 14 £ Fatal bleeding at day 21 Minor bleeding at day 21 Minor bleeding at day 14	Group 1: 10/1614 Group 2: 15/1579 Relative risk: 0.65 (0.29, 1.45) Group 1: 9/1759 Group 2: 3/1740 p value: not significant Group 1: 8 (unsure of denominator) Group 2: 0 (unsure of denominator) p value: not significant Group 1: 10/1614 Group 2: 15/1579 Relative risk: 0.65 (0.29, 1.45) Group 1: 19/1759 Group 2: 10/1740 p value: not significant Group 1: 16 (unsure of denominator) Group 2: 5 (unsure of denominator) p value: not significant	angiography, spiral CT scan or MRI $ DVT diagnosed by compression ultrasonography or venography £ major bleeding defined as: intraocular, spinal/epidural, intracranial or retroperitoneal bleeding; if haemoglobin decreased by >2g/dL; if transfusion of >2 U of blood or significant medical or surgical intervention required; or it resulted in sudden death.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. of dropouts: 8 Age (mean): 68.5 +11.1 M/F: 884/964 Additional risk factors: age >75 33.1%; cancer 4.6%; previous VTE 3.4%; obesity 30.2%; varicose veins 26.4%; hormone therapy 1.8%; chronic heart failure 50.1%; myeloproliferative syndrome 0.3%, chronic respiratory failure 9.5% Group II No. randomised: 1833 No. of dropouts: 7 Age (mean): 68.5 +11.7 M/F: 888/945 Additional risk factors: age >75 33.6%; cancer 5.7%; previous VTE 4.4%; obesity 30.6%; varicose veins 28.9%; hormone therapy 1.6%; chronic heart failure 51.6%; myeloproliferative syndrome 0.5%, chronic respiratory failure 10%				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Mahe et al., 2005 [212] Country of study: France Study design: RCT List who was masked to interventions: patients Evidence level: 1+ Duration of follow-up: 21 days or until discharge (mean study period 13.08 (+6.53 days)	Patient group: Bedridden medical patients (main conditions at inclusion: acute cardiovascular disease 13%, atrial fibrillation 12%, acute pulmonary disease 22%, cancer 14%, sepsis (not pulmonary) 23%) Setting: hospital Inclusion criteria: age >40 hospitalised for <24 hours before randomisation ■ immobilised (unable to walk 10m alone Exclusion criteria: ■ conditions that could increase the risk of haemorrhage (systolic blood pressure >240mmHg, active gastroduodenal ulcer, renal failure – creatinine level >300 µmol/1, prothrombin time <50%, platelet level <50,000/mm3, TCA >control + 10s) ■ conditions requiring full anticoagulation ■ stroke or major surgery within previous 30 days ■ anticoagulant or antiplatelet	Group I LMWH (nadroparin, 0.3ml (7500 AXa IU)) subcutaneously started within 24 hours of hospitalisation and continued for 21 days or until discharge. Group II placebo Additional non-comparative prophylaxis: None	All-cause mortality Fatal pulmonary embolism by total no. deaths confirmed by autopsy	Group 1: 124/1230 Group 2: 128/1244 P value: 0.89 Group 1: 10/63 Group 2: 17/60 P value: 0.26	Funding: "supported by a grant for Independent Research from Sanofi-Choay" Limitations: Only patients appear to be masked to treatment; not reported if allocation to interventions was concealed from patients and participants; only around half of deaths received autopsy Outcomes not reported: pulmonary embolism, DVT, major and minor bleeding, heparin induced

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	therapy within last 7 days ■ pregnancy All patients N: 2474 No. of dropouts: 0 Group I No. randomised: 1230 No. of dropouts: 0 Age (mean): 76.1 M/F: 42% male Additional risk factors: chronic heart failure 26.7%, previous VTE 1.9%, chronic pulmonary disorder 18.5, smoking 15.7%, alcohol abuse 10%, previous stroke 8.5%, recent surgery or trauma (within 1-3 months) 3.7% Other factors: Group II No. randomised: 1244 No. of dropouts: 0 Age (mean): 76.5 M/F: 39% male Additional risk factors: chronic heart failure 24.8%, previous VTE 1.9%, chronic pulmonary disorder 17.6, smoking 14.1%,				thrombocytopenia, post- thrombotic syndrome, quality of life, length of stay Additional outcomes reported: venous thrombosis diagnosed at autopsy, thrombocytopenia (not stated if heparin induced thrombocytopenia) Notes: Study first reported as a letter in 1996 only published as an article in 2005. Study stopped at interim review. Power analysis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	alcohol abuse 8.4%, previous stroke 7.1%, recent surgery or trauma (within 1-3 months) 2.9% Other factors:				determine 3000 patients would be needed to show a difference in mortality. However, the investigators concluded that and additional 600 patients to the interim results of 2474 patients would not lead to a difference. Study screened 35,000 patients for inclusion, main reasons for not being included: ability to walk >10m alone (73%), age <40 years (11%), recent anticoagulation (4.5%)

Study	Miranda 2017[224]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=91)

Study	Miranda 2017[224]
Countries and setting	Conducted in France; Setting: A tertiary care medical centre
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major bleeding: defined as fatal, intracranial or retroperitoneal haemorrphage, necessity of blood transfusion (2 units) or decrease of haemoglobin level greater than 2g/dL.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged greater than 40 years and BMI ≥ 30 kg/m2. Patients had to be hospitalised for the following medical settings: acute congestive heart failure (New York Heart Association class III or IV), acute respiratory failure that did not require ventilator support, acute infection without septic shock, acute rheumatic disorders or inflammatory bowel disease. All levels of obesity from Class 1 to Class 3 were eligible.
Exclusion criteria	Patients were pregnant or breast-feeding women, severe renal insufficiency (defined by clearance <30 mL/min), high risk of bleeding, platelet count below 50x10*9/L, hypersensitivity to heparin or heparin-induced thrombocytopenia type II, and patients already using anticoagulants.
Recruitment/selection of patients	Between September 2013 and April 2015, patients were recruited from 3 different departments: internal medicine, rheumatology and pneumology.
Age, gender and ethnicity	Age - Mean (range): 71 (43-90) years. Gender (M:F): 1/1.2. Ethnicity: Not reported
Further population details	1. BMI : Severely obese (BMI over 35 kg/m2) (Mean BMI: enoxaparin (60mg) group 35.8; enoxaparin (40mg) 37.2). 2. Mobility: Not applicable 3. Renal impairment: No renal impairment (eGFR greater than 30ml/min/1.73m2)
Extra comments	Medical condition: acute infection 50%, acute rheumatic disorders 18%, acute respiratory failure 10.5%, acute congestive heart failure 9%, combined indications 14%
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin. Enoxaparin (60mg) was subcutaneously administered once daily during the first 14 days of hospitalisation at 12pm. Duration 14 days. Concurrent medication/care: After the 14 days, the use of enoxaparin was decided at the discretion of the physician in charge. Indirectness: No indirectness (n=45) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin. Enoxaparin (40mg) was subcutaneously administered once daily during the first 14 days of hospitalisation at 12pm. Duration 14 days. Concurrent medication/care: After the 14 days, the use of enoxaparin was decided at the discretion of the physician in charge. Indirectness: No indirectness

Study	Miranda 2017[224]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (HIGH DOSE) versus ENOXAPARIN (STANDARD DOSE) Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 14 days; Group 1: 0/46, Group 2: 1/45 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 14 days; Group 1: 0/46, Group 2: 0/45 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Heparin-induced thrombocytopenia at up to 90 days from hospital discharge - Actual outcome: Thrombocytopenia at 14 days; Group 1: 0/46, Group 2: 0/45 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge; Pulmonary embolism at 7-90 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	Riess 2010[273] ; Haas 2011 [130] – cancer subgroup; Schellong 2011 [289] – older adults; Tebbe 2011 – heart failure patients [312]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3239)

Countries and setting	Conducted in Germany, Unknown multicentre; Setting: 172 centers
Line of therapy	Not applicable
Duration of study	Intervention time: 8-20 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The incidence of asymptomatic proximal and/or distal DVT was assessed with the use of compression ultrasonography (CUS) of the lower extremity veins at the final visit. Major bleeding was defined as fatal bleeding, clinically overt bleeding associated with a fall in the hemoglobin concentration of more than 20 g L−1 as compared with the baseline hemoglobin concentration, clinically overt bleeding that required transfusion of two or more units of packed red cells or whole blood, or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, retroperitoneal, and pericardial).
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalised medical patients aged at least 70 years, patients had an acute medical illness with a significant decrease in mobility (bedridden or only able to walk short distances) expected for at least 4 days.
Exclusion criteria	Those with immobilization for more than 3 days prior to randomization; those with immobilization due to cast or fracture; those who were expected to undergo a major surgical or invasive procedure within 3 weeks following randomization; those with severe sepsis or a need for ventilatory support (continuous positive airway pressure, oxygen mask, etc. were permitted); those who had received LMWH/heparin for longer than 48 h in the 5 days prior to randomization; those with indications for anticoagulation or thrombolysis; those with a life-expectancy of less than 6 months, or illness with very high acute mortality rate (> 30%); those with acute symptomatic deep vein thrombosis (DVT)/pulmonary embolism (PE); those with acute heparin-induced thrombocytopenia type II (HIT-II) or a history of this; those with acute non-hemorrhagic stroke or a history of this (< 3 months); those with hemorrhagic stroke or intracranial bleeding (< 12 months); those with acute or ongoing intracranial disease; those with a high risk of gastrointestinal bleeding; those with spinal or epidural anesthesia, or lumbar puncture, within the last 12 h; those with uncontrolled hypertension; those with severe liver or renal disease; those with acute endocarditis; and those with known active retinopathy, or intravitreal or other intraocular bleeding.
Recruitment/selection of patients	Patients were recruited in 172 centers between January 2007 and June 2009, and randomized to receive certoparin or UFH
Age, gender and ethnicity	Age - Mean (SD): 78.8 (6.3). Gender (M:F): 1/1.45. Ethnicity: Not reported
Further population details	1. BMI : Not stated 2. Mobility: Mixed 3. Renal impairment: Not stated
Extra comments	Reasons for hospitalisation: Infections and infestations 27.6%, cardiac disorders 22.2%, respiratory, thoracic and mediastinal disorders 17.3%, nervous system disorders 6.6%, gastrointestinal disorders 6.6%, vascular disorders 5.8%

Indirectness of population	No indirectness
Interventions	(n=1626) Intervention 1: Low molecular weight heparin (not licensed in UK) - LMWH (not licensed in UK). Certoparin 3000 U subcutaneously given once daily. The patients in the certoparin treatment group received two additional placebo injections during the day, at 8 hour intervals. Duration 8-20 days. Concurrent medication/care: (Mono-embolex; Novartis Pharma GmbH, Nürnberg, Germany) (n=1618) Intervention 2: Unfractionated heparin - low dose, administered subcutaneously. 5000 IU of UFH subcutaneously given three times daily at 8 hour intervals. Duration 8-20 days. Concurrent medication/care: Liquemin N 5000; Hoffmann-LaRoche AG, Grenzach-Wyhlen, Germany
Funding	Study funded by industry (Funded by Novartis Pharma, Nurnberg, Germany)

CERTIFY - RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CERTOPARIN versus UNFRACTIONATED HEPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 90 days; Group 1: 66/1488, Group 2: 72/1459; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge (not analysed)
- Actual outcome: Symptomatic DVT at 90 days; Group 1: 3/1483, Group 2: 3/1454

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE at 90 days; Group 1: 3/1483, Group 2: 2/1454; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at Unclear; Group 1: 7/1624, Group 2: 10/1615; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Heparin-induced thrombocytopenia at up to 90 days from hospital discharge
- Actual outcome: Heparin-induced thrombocytopenia at Unclear; Group 1: 1/1624, Group 2: 2/1615; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: Venous thromboembolism at 7-90 days from hospital discharge (not analysed)
- Actual outcome: Symptomatic VTE (DVT or symptomatic, non-fatal PE) at 90 days; Group 1: 5/1483, Group 2: 5/1454

Subgroup analysis evaluating cancer patients: Haas 2011 [130]
Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death from any cause at 35 days; Group 1: 159/3096, Group 2: 153/3169; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome: VTE-related death at 35 days; Group 1: 19/2967, Group 2: 30/3057; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 35 days; Group 1: 116/2967, Group 2: 148/3057; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE at 35 days ; Group 1: 10/2967, Group 2: 14/3057; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 35 days; Group 1: 43/3997, Group 2: 15/4001;

Protocol 5: Venous thromboembolism at 7-90 days from hospital discharge (not analysed)
- Actual outcome: Symptomatic VTE at 35 days; Group 1: 18/3997, Group 2: 12/4001

Subgroup analysis evaluating age: Schellong 2011[290]
RESULTS (NUMBERS ANALYSED) FOR COMPARISON: CERTOPARIN (≥80 YEARS OLD) versus UNFRACTIONATED HEPARIN (≥80 YEARS OLD)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 8-20 days; Group 1: 10/680, Group 2: 12/645;

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 8-20 days; Group 1: 53/514, Group 2: 68/518;

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE at 8-20 days; Group 1: 1/652, Group 2: 1/636;

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 8-20 days; Group 1: 4/689, Group 2: 7/676;

RESULTS (NUMBERS ANALYSED) FOR COMPARISON: CERTOPARIN (70 - <80 YEARS OLD) versus UNFRACTIONATED HEPARIN (70 - <80 YEARS OLD)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 8-20 days; Group 1: 10/911, Group 2: 9/899;

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 8-20 days; Group 1: 45/714, Group 2: 55/739;

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE at 8-20 days; Group 1: 6/903, Group 2: 2/893;

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 8-20 days; Group 1: 3/935, Group 2: 3/939;

Subgroup analysis evaluating patients with heart failure: Tebbe 2011[312]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CERTOPARIN versus UNFRACTIONATED HEPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 8-20 days; Group 1: 6/268, Group 2: 0/260;

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 8-20 days; Group 1: 27/217, Group 2: 26/211;

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE at 8-20 days; Group 1: 0/262, Group 2: 0/260;

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 8-20 days; Group 1: 2/277, Group 2: 1/265;

Protocol outcome 5: Heparin-induced thrombocytopenia at up to 90 days from hospital discharge
- Actual outcome: Heparin-induced thrombocytopenia at 8-20 days; Group 1: 1/277, Group 2: 2/265;

Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Samama et al., 1999 [284]	Patient group: Acutely ill medical patients	Group 1 LMWH (20 mg	All-cause mortality (confirmed by:)	Treatment period (days 1-14) Group 1: 15/351	Funding: Supported by grant from

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
MEDENOX study Country of study: International: 60 centres in 9 countries Study design: RCT List who was masked to interventions: Double-blind: Patients and investigators of VTE Evidence level: 1+ Duration of follow-up: 3 months	Setting: General medical ward (most patients were not in an intensive care unit) Inclusion criteria: Medical patients older than 40 years, whose projected stay in hospital was at least six days and not immobilised for more than three days. Patients had to have congestive heart failure (CHF) (New York Association class III or IV), acute respiratory failure that did not require ventilatory support, or one of the following conditions if it was associated with at least one additional risk factor for VT: acute infection with septic shock, acute rheumatic disorders, acute arthritis of the legs, or an acute episode of rheumatoid arthritis in the legs; or an episode of inflammatory bowel disease. The additional risk factors were age >75 years, cancer, previous VT, obesity (BMI >=30 for men and >=28 for women), varicose veins, hormone therapy (antiandrogen or estrogen, except for postmenopausal hormone-replacement therapy) and chronic heart or respiratory failure.	Enoxaparin) 20 mg of enoxaparin (Lovenox, Clexane or Klexane, Rhone- Poulenc Rorer, Antony, France) subcutaneously once daily. 20 mg of enoxaparin in 0.2 ml of water for injectable preparations Start time: within 24 after randomisation End time: Treatment scheduled to last 6 to 14 days in the hospital Group 2 LMWH (40 mg Enoxaparin) 40 mg of enoxaparin (Lovenox, Clexane or Klexane, Rhone- Poulenc Rorer, Antony, France) subcutaneously		Group 2: 12/360 Group 3: 16/362 P: NR Study period (days 1-110) Group 1: 51/351 Group 2: 41/360 Group 3: 50/362 RR (95% CI) as compared with placebo: Group 1: 1.05 (0.71-1.56) p= 0.80 Group 2: 0.83 (0.56-1.21) p=0.31	Rhone- Poulenc Rorer (France) Limitations: A number of patients were not included in the analyses for primary and secondary outcomes. Reasons below Outcomes not reported: pulmonary hypertension, heparin-induced thrombocytopenia; post thrombotic syndrome, quality of life, length of stay Additional outcomes reported: Local reaction at injection site (hematoma>5 cm in diameter); any
			Fatal pulmonary embolism (confirmed by autopsy)	Primary outcome (VT between days 1-14) Group 1: 0/287 Group 2: 0/291 Group 3 0/288 P: NR Secondary outcome (VT between days 1-110) Group 1: 1/263 Group 2: 2/272 Group 3: 1/263 P value: NR	
			Symptomatic pulmonary embolism (confirmed by: not reported)	Reported in text: by day 14 Group 1: 1/287 Group 2: 0/291 Group 3: 3/288 P value: NR	
			Pulmonary embolism, asymptomatic or symptomatic	Primary outcome (VT between days 1-14) Group 1: 1/287	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		once daily. 40 mg of enoxaparin in 0.2 ml of water for injectable preparations Start time: within 24 after randomisation	(confirmed by high-probability lung scanning, pulmonary angiography, or helical computed tomography or at autopsy)	Group 2: 0/291 Group 3 3/288 P value: NR Secondary outcome (VT between days 1-110) Group 1: 1/263 Group 2: 0/272 Group 3: 3/263 P value: NR	thrombocytopaenia Notes: * (description: If bleeding was overt and was associated with the need for transfusion of two or more units of packed red cells or whole blood or with a decrease in the haemoglobin concentration of 2.0 g per decilitre or more from baseline or if bleeding was retroperitoneal, intracranial, or fatal) Reasons for patients not evaluated for
	Exclusion criteria: Women of childbearing age if pregnant, breast-feeding or not using contraception.	End time: Treatment scheduled to last 6 to 14 days in the hospital			
	Other exclusions were: stroke or major surgery within the previous three months, contraindications to use of iodinated contrast medium; known thrombophilia; a serum creatinine concentration >1.7 mg/dl, intubation, HIV, uncontrolled arterial hypertension, active peptic ulcer, bacterial endocarditis, or other conditions that could increase the risk of haemorrhage; hypersensitivity to heparin or heparin-induced thrombocytopenia; or platelet count < 100,000/mm3 a prolonged activated partial-thromboplastin time, a prothrombin ratio of less than	Group 3 (Placebo) Placebo (0.2 ml of isotonic water) Start time: within 24 after randomisation End time: Treatment scheduled to last 6 to 14 days in the hospital	Symptomatic DVT (confirmed by: not reported)	Primary outcome (VT between days 1-14) Group 1: 3/287 Group 2: : 1/291 Group 3: 2/288 Secondary outcome (VT between days 1-110) Group 1: 6/263	
		Additional non-comparative prophylaxis: Elastic bandages or support stockings, and physiotherapy were used	DVT, asymptomatic or symptomatic (confirmed by systematic ascending contract venography of the legs between days 6 and 14, or earlier if	Group 2: : 3/272 Group 3: 4/263 Primary outcome (VT between days 1-14) Group 1: 42/287 Group 2: : 16/291 Group 3: 41/288	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	50 percent, or an international normalized ratio of more than 1.2. Patients who required anticoagulant therapy and those who received any type of anticoagulant therapy for more than 48 hours. All patients N: 1,102 No. of dropouts: There were 236 patients not evaluated for the primary outcome (VT defined as DVT, PE, or both between days 1 and 14) and 71 patients were not evaluated for the secondary outcome (VT between days 1 and 110) reasons included in table 1. Group 1 (20 mg Enoxaparin) No. randomised: 364 No. of dropouts No. evaluated for primary outcome: Evaluated: 287 (78.8%) Not evaluated: 77 (21.2%) No. evaluated for secondary outcome: Evaluated: 263 (72.3%) Not evaluated: 25 (6.9%) Age (mean +/- SD): 72.9 +/- 10.1 M/F: 187/176 Reasons for hospitalisation-no. (%): NYHA class III CHF: 76 (20.9)	according to the usual practice at each centre. Throughout the treatment period, intramuscular injections and treatment with nephrotoxic substances, particularly nephrotoxic antibiotics, were not permitted. Centres were advised to avoid giving patients nonsteroidal anti-inflammatory drugs	thrombosis was clinically suspected. If venography was infeasible venous ultrasonography was performed.)	RR (95% CI) as compared with placebo: Group 1: 1.05 (0.71-1.57) p= 0.81 Group 2: 0.40 (0.23-0.69) p<0.001 Secondary outcome (VT between days 1-110) Group 1: 44/263 Group 2: : 17/272 Group 3: 42/263 RR (95% CI) as compared with placebo: Group 1: 1.07 (0.73-1.58) p= 0.81 Group 2: 0.40 (0.23-0.69) p<0.001	primary outcome, analysis of VTE at 14 days: death 28/236; patient's refusal 62/236, investigator's decision 62/236, venography technically unfeasible 12/236, venogram could not be evaluated 72/236, unknown, venography not performed 10/236 Reasons for patients not evaluated for secondary outcome, analysis of VTE at 110 days: death 61/71; loss to follow up or scheduled visit before 90 days 10/71
			Thigh DVT Reported in table described as proximal deep- vein thrombosis. Confirmed by see above	Primary outcome (VT between days 1-14) Group 1: 13/287 Group 2: 5/291 Group 3: 14/288 RR (95% CI) as compared with placebo: Group 1: 0.93 (0.45-1.94) p=0 1 Group 2: 0.35 (0.13-0.97) p=0.04 Secondary outcome (VT between days 1-110) Group 1:14/263 Group 2: 6/272 Group 3: 17/263 RR (95% CI) as compared with placebo: Group 1: 0.83 (0.42-1.64) p= 0.71 Group 2: 0.34 (0.14-0.86) p=0.02	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	NYHA class IV CHF: 44 (12.1) Acute respiratory failure: 192 (52.9) Acute infectious disease: 194 (53.4) Acute rheumatic disorder: 40 (11.0) Inflammatory bowel disease: 1 (0.3) Additional risk factors- no. (%): Age>75 years: 172 (47.4) Cancer (previous or current): 56 (15.4) History of VT: 35 (9.6) Obesity: 79 (21.8) Varicose veins: 88 (24.2) Hormone therapy: 8 (2.2) Chronic heart failure: 106 (29.2) Chronic respiratory failure: 197 (54.3) >=2 Risk factors 241 (66.4) Group 2 (40 mg Enoxaparin) No. randomised: 367 No. of dropouts: No. evaluated for primary outcome: Evaluated: 291 (79.3) Not evaluated 76 (20.7%) No. evaluated for secondary outcome: Evaluated: 272 (74.1%) Not evaluated: 20 (5.4%)		Calf DVT Reported in table described as distal deep-vein thrombosis. Confirmed by see above	Primary outcome (VT between days 1-14) Group 1: 30/287 Group 2: : 11/291 Group 3: 27/288 G Secondary outcome (VT between days 1-110) Group 1: 31/263 Group 2: 12/272 Group 3: 27/263	
			Fatal bleeding (description:)	Treatment period (days 1-14) Group 1: 0/351 Group 2: 1/360 Group 3: 0/362 P value not reported Study reports NS difference between groups Study period (days 1-110) Group 1: 1/351 Group 2: : 2/360 Group 3: 0/362 P value not reported Study reports NS difference between groups	
			Major bleeding *	Treatment period (days 1-14) Group 1: 1/351 Group 2: 6/360 Group 3: 4/362 P value not reported Study reports difference NS Study period (days 1-110) Group 1: 4/351 Group 2: 12/360	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 73.1 +/- 10.8 M/F: 171/196 Reasons for hospitalisation-no. (%): NYHA class III CHF: 103 (28.1) NYHA class IV CHF: 26 (7.1) Acute respiratory failure: 195 (53.1) Acute infectious disease: 197 (53.7) Acute rheumatic disorder: 28 (7.6) Inflammatory bowel disease: 3 (0.8) Additional risk factors- no. (%): Age>75 years: 185 (50.4) Cancer (previous or current): 45 (12.3) History of VT: 30 (8.2) Obesity: 72 (19.6) Varicose veins: 98 (26.7)			Group 3: 7/362 P value not reported Study reports difference NS	
			Minor bleeding (description: Overt but did not meet the other criteria for major bleeding)	Treatment period (days 1-14) Group 1: 40/351 Group 2: 39/360 Group 3: 27/362 P value not reported Study reports difference NS Study period (days 1-110) Group 1: 57/351 Group 2: 51/360 Group 3: 45/362 P value not reported Study reports difference NS	
			Venous thromboembolic events (defined as DVT, PE or both)	Primary outcome (VT between days 1-14) Group 1: 43/287 Group 2: 16/291 Group 3: 43/288 RR (95% CI) as compared with placebo: Group 1: 1.02 (0.70-1.51) p= 0.90 Group 2: 0.37 (0.22-0.63) p<0.001 Secondary outcome (VT between days 1-110) Group 1 (20 mg Enoxaparin):46/263 Group 2: 19/272 Group 3: 45/263 RR (95% CI) as compared with placebo: Group 1: 1.02 (0.70-1.49) p=	
	Hormone therapy: 5 (1.4) Chronic heart failure: 123 (33.5) Chronic respiratory failure: 195 (53.1) >=2 Risk factors: 245 (66.8) Group 3 (Placebo) No. randomised: 371 No. of dropouts: No. evaluated for primary outcome: Evaluated: 288 (77.6 %) Not evaluated: 83 (22.4%)		DVT and PE		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. evaluated for secondary outcome: Evaluated: 263 (70.9%) Not evaluated: 26 (7.0 %) Age (mean): 74.1 +/- 10.6 M/F: 192/178 Reasons for hospitalisation-no. (%): NYHA class III CHF: 95 (25.7) NYHA class IV CHF: 32 (8.6) Acute respiratory failure: 202 (54.6) Acute infectious disease: 193 (52.2) Acute rheumatic disorder: 32 (8.6) Inflammatory bowel disease: 1 (0.3)			0.91 Group 2: 0.41 (0.25-0.68) p<0.001 Primary outcome (VT between days 1-14) Group 1: 1/287 Group 2: 0/291 Group 3 (Placebo): 1/288 Secondary outcome (VT between days 1-110) Group 1: 1/263 Group 2: 0/272 Group 3: 1/263	
	Additional risk factors- no. (%): Age>75 years: 197 (53.2) Cancer (previous or current): 56 (15.1) History of VT: 39 (10.5) Obesity: 71 (19.2) Varicose veins: 93 (25.1) Hormone therapy: 9 (2.4) Chronic heart failure: 124 (33.5) Chronic respiratory failure: 197 (53.2) >=2 Risk factors: 247 (66.8)		Thrombocytopaenia (Thrombocytopenia was defined as a decrease in the platelet count of less than 100,000/mm3. Thrombocytopenia was considered severe if the platelet count was less than 50,000/mm3	Treatment period (days 1-14) Group 1: 10/351 (4 related to treatment) Group 2: 8/360 (2 related to treatment) Group 3: 3/362 (8 related to treatment) P value not reported Study reports NS difference Severe thrombocytopenia: Group 1: 0/351 Group 2: 0/360 Group 3: 3/362 Study period (days 1-110) Thrombocytopenia: Group 1: 10/351 Group 2: 8/360 Group 3: 13/362 Severe thrombocytopenia: Group 1: 0/351 Group 2: 0/360	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
				Group 3: 3/362 P value not reported Study reports NS difference	

Study	Schellong 2010[291]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=337)
Countries and setting	Conducted in Germany, Unknown multicentre; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention time: 10 (2 days)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT - assessed with the use of complete compression ultrasound (CCUS) of the lower extremity veins.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients of either gender > 40 years, hospitalisation due to an acute non-surgical disease, significant recent decrease in mobility (completely bedridden or only able to walk short distances with the support of a nurse)
Exclusion criteria	Women of childbearing age unless they were post-menopausal or using a highly effective method of birth control, pregnancy or lactation, indication for anticoagulant or thrombolytic therapy, major surgery or invasive procedure within 4 weeks prior to randomisation or expected within 2 weeks after randomisation, immobilisation due to cast or fracture of the lower extremity or > 3 days prior to randomisation, heparin administration for more than 36 hour in the period prior to randomisation, acute ischemic stroke, haemorrhagic stroke, or other intracranial bleeding (acute or within the last 12 months), life expectancy <1, endocarditis, history of or current HIT type II, retinopathy, recent history of addictive disorder
Recruitment/selection of patients	February 2006-December 2007
Age, gender and ethnicity	Age - Mean (SD): 70.6 (12.3) years. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. BMI : Not stated 2. Mobility: Totally immobile 3. Renal impairment: Not stated
Extra comments	Mean duration of 8.5 ± 2.1 days in both groups
Indirectness of population	No indirectness

Study	Schellong 2010[291]
Interventions	(n=163) Intervention 1: Low molecular weight heparin (not licensed in UK) - LMWH (not licensed in UK). Single daily dose 3000 U certoparin during the treatment period. Duration 10 (2) days. Concurrent medication/care: N/A (n=174) Intervention 2: Unfractionated heparin - low dose, administered subcutaneously. 7500 IU unfractionated heparin (UFH) during the treatment period. Duration 10 (2) days. Concurrent medication/care: N/A
Funding	Study funded by industry (Study was funded by Novartis Pharma, Nurnberg, Germany.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CERTOPARIN versus UNFRACTIONATED HEPARIN Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality (VTE related and unrelated death) at 90 days; Group 1: 8/163, Group 2: 12/172; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 90 days; Group 1: 10/103, Group 2: 23/100; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome: PE at 90 days; Group 1: 1/103, Group 2: 2/100; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Heparin-induced thrombocytopenia at up to 90 days from hospital discharge - Actual outcome: Heparin-induced thrombocytopenia at 90 days; Group 1: 0/163, Group 2: 0/172; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Major bleeding at up to 45 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

H.14 Cancer

Study	CONKO-004 trial: Pelzer 2015[257]

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=312)
Countries and setting	Conducted in Germany; Setting: Multicentre and group-sequential trial in patients with APC who were treated with first-line chemotherapy in an outpatient setting.
Line of therapy	1st line
Duration of study	Intervention + follow up: Primary endpoint was event rate within first 3 months; enrollment was between April 2004 and Jaunary 2009
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: In cases of symptomatic disorders with suspected venous thrombosis or embolic events (e.g. unilateral oedema, local tumour/dolor/colour, and/or acute distress), further diagnostic workup (further to cancer workup with staging CT or MRI) was required.
Stratum	Overall:
Subgroup analysis within study	Stratified then randomised: Stratified by Karnofsky performance status and kidney function. patients with KPS ≥80% and notmal kidney function received GFFC therapy. Patients with KPS ≤80% and/or increased creatinine plasma levels started gemcitabine therapy. Patients were also stratified according to tumor stage, type of tumor, and prior thrombosis.
Inclusion criteria	Histological or cytological pancreatic carcinoma, stage IV A, b, no preceding radio or chemotherapy of the primarius or the reference lesions, Karnofsky performance status ≥ 60%, measurable tumor lesion by spiral CT or MRT not older than 14 days, no deep venous thrombosis within the last 2 years, patient compliance and geographical proximity of the residence, which make an adequate follow up possible, sufficient bone marrow reserve: leukocyte ≥ 3.5 × 109 /l, thrombocyte ≥ 100 × 109 /l, signed informed consent, minimum age of 18 years, women/men must provide sufficient pregnancy prevention
Exclusion criteria	Pre-existing indication for anti-coagulation of other reason, bleeding in the last 2 weeks or increased bleeding risk (e.g. serious coagulating disturbance, active stomach or intestine ulcera, or had operational interferences in the last 2 weeks), body weight < 45 kg and/or > 100 kg, pregnancy or insufficient preventing methods in the study process, serious illness, which are incompatible with a study participation, hypersensitivity to study drugs, patients with serious kidney malfunction (Creatinin clearance <30 ml/min)
Recruitment/selection of patients	Enrollment was between April 2004 and January 2009
Age, gender and ethnicity	Age - Median (range): Enoxaparin: 62 (32-81); observation: 63 (27-83). Gender (M:F): Enoxaparin: 91:69; observation: 94:58. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Median (range) BMI for Enoxaparin vs observation: 24.3 (15.2-43.0) vs 23.8 (16-39.2)). 2. Chemotherapy: Chemotherapy (GFFC or GEM). 3. Renal impairment: Mixed 4. Tumour: Solid (Advanced

	Pancreatic Cancer: pancreatic carcinoma, stage IV A, b).
Indirectness of population	No indirectness
Interventions	(n=160) Intervention 1: Low molecular weight heparin - Enoxaparin. Enoxaparin at half therapeutic dose. Duration 3 months. Concurrent medication/care: Patients with KPS <80 % and increased creatinine plasma levels (>1.3 mg/dl) received the current standard therapy (gemcitabine 1 g/m2 (30 min), d1, 8, 15; q4w)Patients with KPS >80% and normal kidney function receive GFFC + LMWH (gemcitabine 1 g/m2 (30 min), cisplatin 30 mg/m2 (90 min), 5-fluorouracil 750 mg/m2 (24 h), folinic acid 200 mg/m2 (30 min), d1, 8; q3w (n=152) Intervention 2: No treatment - Usual care. Usual care. Duration 3 months. Concurrent medication/care: Patients with KPS <80 % and increased creatinine plasma levels (>1.3 mg/dl) received the current standard therapy (gemcitabine 1 g/m2 (30 min), d1, 8, 15; q4w) Patients with KPS >80% and normal kidney function receive GFFC + LMWH (gemcitabine 1g/m2 (30 min), cisplatin 30 mg/m2 (90 min), 5-fluorouracil 750 mg/m2 (24 h), folinic acid 200 mg/m2 (30 min), d1, 8; q3w
Funding	Other author(s) funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: Symptomatic DVT only (not analysed) at 3 months; Group 1: 8/160, Group 2: 17/152
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not fully reported therefore downgraded once for indirectness ; Blinding details: Authors state that the open, nonblinded design may have resulted in patient and physician bias - ethical reasons. Also VTE diagnoses often established on nonspecific symptoms. This may have led to additional physician bias. ; Group 1 Number missing: 7, Reason: Lost to follow-up; Group 2 Number missing: 10, Reason: Lost to follow-up

Protocol outcome 2: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE (symptomatic, no confirmation details) at 3 months; Group 1: 0/160, Group 2: 3/152
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not fully reported therefore downgraded once for indirectness ; Blinding details: Authors state that the open, nonblinded design may have resulted in patient and physician bias - ethical reasons. Also VTE diagnoses often established on nonspecific symptoms. This may have led to additional physician bias. ; Group 1 Number missing: 7, Reason: Lost to follow-up; Group 2 Number missing: 10, Reason: Lost to follow-up

Protocol outcome 3: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Major bleeding events at 3 months; Group 1: 7/160, Group 2: 5/152 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: Lost to follow-up; Group 2 Number missing: 10, Reason: Lost to follow-up	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	**Larocca 2012[187]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=342)
Countries and setting	Conducted in Israel, Italy; Setting: 62 centres in Italy and Israel
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months follow-up
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Not all outcome assessment methods reported - major and minor bleeding reported.
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis: The aim of the substudy was to compare the effectiveness and safety of ASA and LMWH as antithrombotic prophylaxis in patients receiving lenalidomide based induction and consolidation therapy.
Inclusion criteria	Previously untreated patients with NDMM, aged between 18 and 65 years, enrolled in the phase 3 trial were assessed for eligibility to be enrolled in the substudy. Eligible patients had no history of DVT or arterial thromboembolic events within the past 12 months, no clear indication or contraindication for antiplatelet or anticoagulant therapy, had no active bleeding, and were not considered to be at high risk of bleeding.
Exclusion criteria	Exclusion criteria were clear indication or contraindication for a specific antiplatelet or anticoagulant therapy (eg, cardiac arrhythmia, cardiac ischemia, or previous history of arterial or venous thromboembolism), and active bleeding or high risk of bleeding, recent orthopedic surgery or vertebroplasty, immobilisation, allergy to ASA, concomitant thromboembolism at diagnosis, concomitant disseminated intravascular coagulation, inherited thrombophilic

	abnormalities, previous history of coronary ischemic disease or angioplasty
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Median (range): For ASA and LMWH respectively - 57 and 58 (no range reported). Gender (M:F): For ASA and LMWH respectively - 87:89; 99:67. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Chemotherapy: Chemotherapy (See treatment descriptions for details). 3. Renal impairment: Not applicable 4. Tumour: Haematological (newly diagnosed multiple myeloma (NDMM)).
Extra comments	Patients with newly diagnosed multiple myeloma (NDMM).
Indirectness of population	No indirectness
Interventions	(n=176) Intervention 1: Aspirin. ASA 100mg/day orally. Duration Prophylaxis was administered during the 4 cycles of Rd therapy and the 6 cycles of MPR consolidation. Patients who were assigned to the Mel200 consolidation arm stopped thromboprophylaxis at this point. Antithrombotic prophylaxis was discontinued in any patient who developed DVT, PE, arterial thrombosis, or any acute cardiovascular or bleeding event or patient who had a platelet count of <50 000/microlitres. Patients attended clinic study visits every 2 weeks during the first 2 cycles of Rd or MPR, then every 4 weeks for the last 2 cycles of Rd and the last 4 cycles of MPR to assess the effectiveness and safety of treatment. (Subsequently, patients attended visits at the physician's discretion, and the incidence of thromboembolism in the absence of prophylaxis was also evaluated.). Concurrent medication/care: All patients received induction with lenalidomide plus low-dose dexamethasone (Rd) treatment comprising four 28-day cycles of lenalidomide (25 mg/d orally for 21 days) in combination with dexamethasone (40 mg/d orally on days 1, 8, 15, and 22), followed by cyclophosphamide (4 g/m2) for stem cell mobilization and collection before entering the consolidation phase with either MPR or Mel200. The MPR consolidation phase comprised six 28-day cycles of lenalidomide 10 mg/d for 21 days, melphalan 0.18 mg/kg for 4 days, and prednisone 2 mg/kg for 4 days. (n=166) Intervention 2: Low molecular weight heparin - Enoxaparin. Enoxaparin 40mg/d subcutaneously. Duration rophylaxis was administered during the 4 cycles of Rd therapy and the 6 cycles of MPR consolidation. Patients who were assigned to the Mel200 consolidation arm stopped thromboprophylaxis at this point. Antithrombotic prophylaxis was discontinued in any patient who developed DVT, PE, arterial thrombosis, or any acute cardiovascular or bleeding event or patient who had a platelet count of <50 000/microlitres. Patients attended clinic study visits every 2 weeks during the first 2 cycles of Rd or MPR, then every 4 weeks for the last 2 cycles of Rd and the last 4 cycles of MPR to assess the effectiveness and safety of treatment. (Subsequently, patients attended visits at the physician's discretion, and the incidence of thromboembolism in the absence of prophylaxis was also evaluated.). Concurrent medication/care: ll patients received induction with lenalidomide plus low-dose dexamethasone (Rd) treatment comprising four 28-day cycles of lenalidomide (25 mg/d orally for 21 days) in combination with dexamethasone (40 mg/d orally on days 1, 8, 15, and 22), followed by cyclophosphamide (4 g/m2) for stem cell mobilization and collection before entering the

	consolidation phase with either MPR or Mel200. The MPR consolidation phase comprised six 28-day cycles of lenalidomide 10 mg/d for 21 days, melphalan 0.18 mg/kg for 4 days, and prednisone 2 mg/kg for 4 days.
Funding	Equipment / drugs provided by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ENOXAPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Sudden, otherwise unexplained death (presumed to be related to PE, acute myocardial infarction, or stroke) at During first 6 months of follow-up; Group 1: 0/176, Group 2: 0/166
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - Additional selection bias because only patient with standard risk of VTE aged <65 years were included; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT objectively confirmed symptomatic only (not analysed) at During first 6 months of follow-up; Group 1: 2/176, Group 2: 2/166
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - Additional selection bias because only patient with standard risk of VTE aged <65 years were included; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE no further details at During first 6 months of follow-up; Group 1: 3/176, Group 2: 0/166
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - Additional selection bias because only patient with standard risk of VTE aged <65 years were included; Indirectness of outcome: Serious indirectness, Comments: Unclear method of confirmation; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding defined as fatal bleeding, symptomatic bleeding in a crucial area or organ, bleeding causing a reduction in hemoglobin concentration of 2g.dL or that necessitated transfusion of ≥2 units of whole blood or red cells. at During first 6 months of follow-up; Group 1: 0/176, Group 2: 0/166
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - Additional selection bias because only patient with standard risk of VTE aged <65 years were included; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital

	discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	**Levine 1994[206]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=315)
Countries and setting	Conducted in Canada, Italy; Setting: Multicentre, international
Line of therapy	1st line
Duration of study	Intervention time: From the start of chemotherapy or within 4 weeks and continued until 1 week after termination of chemotherapy
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: By centre and presence or absence of central-venous catheter.
Inclusion criteria	Metastatic breast carcinoma and had been receiving first-line or second-line chemotherapy for 4 weeks or less.
Exclusion criteria	Eastern Cooperative Oncology Group performance status of 3 or more, an underlying bleeding disorder or active peptic ulcer disease, direct bilirubin more than twice normal, an INR of 1.3 or more, a platelet count below 50 x 10/L, a history of alcohol abuse, overt brain metastases, presence of an underlying psychiatric or affective disorder, requirement for long-term oral anticoagulant therapy, expected survival of less than 3 months, concurrent receipt of hormonal therapy, and inability to attend follow-up visits for geographical reasons.
Recruitment/selection of patients	Recruitment began in June 1989 and stopped in June 1992
Age, gender and ethnicity	Age - NR: NR. Gender (M:F): NR. Ethnicity: NR
Further population details	1. BMI : Not applicable 2. Chemotherapy: Chemotherapy 3. Renal impairment: Not applicable 4. Tumour: Solid (Metastatic breast cancer).
Indirectness of population	No indirectness
Interventions	(n=154) Intervention 1: Vitamin K antagonists - Warfarin. Very low dose warfarin 1mg daily for 6 weeks. At 6 weeks dose adjusted to produce a very slight anticoagulant effect corresponding to an INR of 1.3-1.9. Duration of chemotherapy plus 7 days, mean (SD) 199 (126). Concurrent medication/care: Chemotherapy

	(n=161) Intervention 2: No treatment - Placebo. Identical inert tablet. Sham INR's generated to reflect fluctuations in dose-response observed in warfarin group and number of inert tablets given accordingly. Duration of chemotherapy plus 7 days, mean (SD) 188 (137) days. Concurrent medication/care: Chemotherapy
Funding	Academic or government funding (Supported by a grant-in-aid from the National Cancer Institute of Canada)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN versus PLACEBO Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: Survival at Approximately 6 months; Group 1: 87/152, Group 2: 99/159 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome: Symptomatic DVT only (extracted but not analysed) at Approximately 6 months; Group 1: 0/152, Group 2: 6/159 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome: Symptomatic PE confirmed by ventilation-perfusion lung scanning at Approximately 6 months; Group 1: 1/152, Group 2: 1/159 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Major bleeding associated with a fall in hemoglobin of 20 g/dL or more, or a need for transfusion of 2 or more units of blood, or if it was retroperitoneal or intracranial. at Approximately 6 months; Group 1: 1/152, Group 2: 2/159 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	Levine 2012[207]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=125)
Countries and setting	Conducted in Canada, USA; Setting: Six sites in Canada and eight in the USA participated
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks (84 days)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major bleeding and DVT defined and method described.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects were eligible if they were over 18 years of age and receiving either first-line or second-line chemotherapy for advanced or metastatic lung, breast, GI (colon, rectum, pancreas, stomach), bladder, cancer of unknown origin, ovarian or prostate cancer, myeloma or selected lymphomas, if they were able to begin study medication within 6 weeks of starting either first-line or second-line chemotherapy, and if the expected course of chemotherapy was 90 days or more.
Exclusion criteria	Women of childbearing potential who were unwilling or unable to use an acceptable method of contraception to avoid pregnancy for the entire study period, who were using a prohibited contraceptive method, or who were pregnant or breastfeeding; prior history of documented DVT or PE; active bleeding or high risk for bleeding; having a serious hemorrhage that had required hospitalization, transfusion or surgical intervention within 4 weeks of study entry; familial bleeding diathesis; overt metastasis of cancer to the brain; expected survival of <6 months or an Eastern Cooperative Oncology Group performance status of >3; candidate for bone marrow transplantation within the 12-week treatment period or 30-day follow-up period; uncontrolled hypertension (systolic blood pressure of >200 mmHg and/or diastolic blood pressure of >110 mmHg); presence of a coagulopathy; alanine aminotransferase greater than three times the upper limit of normal (ULN); total bilirubin greater than two times the ULN; calculated creatinine clearance of <30 mL min)^-1; and requiring long-term oral anticoagulant therapy, > 165mg daily aspirin, clopidogrel, cilostazol, or aspirin–dipyridamole.
Recruitment/selection of patients	Details not reported
Age, gender and ethnicity	Age - Median (range): Apixaban 5 mg: 57 (41–67), Apixaban 10 mg: 60 (39–76), Apixaban 20 mg: 64 (25–86), Placebo: 59 (20–82). Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Chemotherapy: Chemotherapy 3. Renal impairment: Not applicable 4. Tumour: Mixed (Mixture of solid tumours, heamatologic and liver metastases).

Extra comments	See inclusion criteria. The trial was a phase II dose-ranging/tolerability study
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: No treatment - Placebo. All subjects took four tablets orally once daily; these consisted of a combination of apixaban and matching placebo tablets for the apixaban treatment groups, or all placebo tablets for the placebo treatment group (such that the study supplies for subjects in all treatment groups were identical in appearance). Duration Each subject was to be given study tablets daily for 12 weeks, beginning within 4 weeks of the date on which the first-line or second-line chemotherapy was begun. Mean duration 69.6 days (range 7-91). Concurrent medication/care: Chemotherapy - various regimens. Initially, subjects who had received bevacizumab within the previous 6 months were not eligible to participate in the study. During the trial, the protocol was amended to allow patients receiving bevacizumab to participate, provided that it was used for indications approved by local country law. Sunitinib or sorafenib were not permitted within 3 months of subjects being treated with the study drug. (n=95) Intervention 2: Apixaban. 5mg, 10mg or 20mg Apixaban. All subjects took four tablets orally once daily; these consisted of a combination of apixaban and matching placebo tablets for the apixaban treatment groups, or all placebo tablets for the placebo treatment group (such that the study supplies for subjects in all treatment groups were identical in appearance). Duration Each subject was to be given study tablets daily for 12 weeks, beginning within 4 weeks of the date on which the first-line or second-line chemotherapy was begun. Median duration 84 days. Range 14-92 days. Concurrent medication/care: Initially, subjects who had received bevacizumab within the previous 6 months were not eligible to participate in the study. During the trial, the protocol was amended to allow patients receiving bevacizumab to participate, provided that it was used for indications approved by local country law. Sunitinib or sorafenib were not permitted within 3 months of subjects being treated with the study drug.
Funding	Study funded by industry (The study was sponsored by Bristol-Myers Squibb and Pfizer Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death from any cause at 114-121 days (30 days after treatment completion); Group 1: 1/93, Group 2: 2/29
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: Symptomatic DVT only. Confirmed with compression ultrasound or venography. at 114-121 days (30 days after treatment completion); Group 1: 0/93,

Group 2: 3/29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome: Symptomatic PE confirmed by spiral CT or ventilation/perfusion lung scan. at 114-121 days (30 days after treatment completion); Group 1: 0/93, Group 2: 1/29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Clinically overt, bleeding that resulted in a decrease in haemoglobin of 20g L-1 or more; bleeding that led to a transfusion of two or more units of packed red blood cells or whole blood; bleeding that occurred in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; or bleeding that contributed to death. at 114-121 days (30 days after treatment completion); Group 1: 2/93, Group 2: 1/29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 Protocol outcome 5: Clinically relevant non-major bleeding at up to 45 days from hospital discharge - Actual outcome: Bleeding not meeting the criteria for major bleeding but that in routine clinical practice would be considered to be relevant and not trivial by a patient or physician at 114-121 days (30 days after treatment completion); Group 1: 4/93, Group 2: 0/29 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	**Palumbo 2011[249]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=667)
Countries and setting	Conducted in Italy; Setting: 84 centres during May 2006 to January 2009
Line of therapy	Adjunctive to current care

Duration of study	Intervention + follow up: Median follow-up time was 24.9 months; primary endpoint measured within 6 months and during entire follow-up
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Only bleeding outcome assessment method reported
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Stratified by age ≤65 or >65 received different chemotherapy regimes. Only patients receiving thalidomide-based regimes in both trials were eligible for this substudy.
Inclusion criteria	Previously untreated patients with myeloma. In one of the two studies, patients age 65 years were randomly assigned to bortezomib (1.3 mg/m2 on days 1, 4, 8, and 11), thalidomide (200 mg/d), and dexamethasone (320 mg) or to thalidomide and dexamethasone in each 21-day cycle for three courses as induction therapy before autologous transplantation. In the other study, patients age 65 years were randomly assigned to bortezomib (1.3 mg/m2 on days 1, 8, 15, and 22), melphalan (9 mg/m2 on days 1 to 4), prednisone (60 mg/m2 on days 1 to 4), and thalidomide (50 mg/d) for nine courses followed by continuous therapy with bortezomib (1.3 mg/m2 every 15 days) and thalidomide (50 mg/d) or to bortezomib, melphalan, and prednisone for nine courses without any further continuous treatment. Patients randomly assigned to receive bortezomib, melphalan, and prednisone did not receive any antithrombotic prophylaxis. Patients receiving thalidomide-based regimens in both trials were eligible for the substudy.
Exclusion criteria	Exclusion criteria were allergy or intolerance to study drugs, clear indication or contraindication for a specific antiplatelet or anticoagulant therapy (eg, cardiac arrhythmia, cardiac ischemia, or previous history of arterial or venous thromboembolism), and active bleeding or high risk of bleeding.
Recruitment/selection of patients	Patients receiving thalidomide-based regimens in both of the two cancer trials from which this substudy was carried out were eligible for the substudy.
Age, gender and ethnicity	Age - Median (IQR): For ASA, warfarin and LMWH (enoxaparin): 61 (55-66); 60 (54-66); 62 (55-66). Gender (M:F): 362:297. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Chemotherapy: Chemotherapy (Thalidomide containing regimens). 3. Renal impairment: Not applicable 4. Tumour: Haematological (Myeloma).
Extra comments	.This was a common sub-study of two simultaneous chemotherapy phase III trials using thalidomide-based regimens in previously untreated patients with myeloma (Cavo 2010, Palumbo 2010).
Indirectness of population	No indirectness
Interventions	(n=224) Intervention 1: Aspirin. 100mg/day orally. Duration Administered during the first 3 cycles of induction therapy. Concurrent medication/care: Patients would have been on a thalidomide regimen containing arm from one of the two main trials.

	(n=222) Intervention 2: Vitamin K antagonists - Warfarin. 1.25mg/day orally. Duration Administered during the first 3 cycles of induction therapy. Concurrent medication/care: Patients would have been on a thalidomide regimen containing arm from one of the two main trials. (n=221) Intervention 3: Low molecular weight heparin - Enoxaparin. 40mg/day subcutaneously. Duration Patients would have been on a thalidomide regimen containing arm from one of the two main trials. Concurrent medication/care: Administered during the first 3 cycles of induction therapy
Funding	Other (Mixed - some authors funded by industry and some research funding)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus WARFARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Sudden, otherwise unexplained death (presumed to be a result of PE, acute myocardial infarction, or stroke). at 6 months; Group 1: 1/220, Group 2: 0/220
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT symptomatic only (not analysed) at 6 months; Group 1: 8/220, Group 2: 14/220
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: 4, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE symptomatic. Pulmonary embolism was identified by performing a high-probability lung scan; an intermediate-probability lung scan in the presence of objectively confirmed deep vein thrombosis; a diagnostic spiral computed tomography scan; diagnostic pulmonary angiography; or diagnostic transesophageal echocardiography. at 6 months; Group 1: 4/220, Group 2: 4/220
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: 4, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding defined as fatal bleeding, symptomatic bleeding in a crucial area of organ, bleeding causing a reduction in haemoglobin concentration of >2g/dL or necessitating transfusion of > 2 units of whole blood or RBC cells. at 6 months; Group 1: 3/220, Group 2: 0/220
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ENOXAPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Sudden, otherwise unexplained death (presumed to be a result of PE, acute myocardial infarction, or stroke). at 6 months; Group 1: 1/220, Group 2: 1/219
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT symptomatic only (not analysed) at 6 months; Group 1: 8/220, Group 2: 6/219
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: 4, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE symptomatic. Pulmonary embolism was identified by performing a high-probability lung scan; an intermediate-probability lung scan in the presence of objectively confirmed deep vein thrombosis; a diagnostic spiral computed tomography scan; diagnostic pulmonary angiography; or diagnostic transesophageal echocardiography. at 6 months; Group 1: 4/220, Group 2: 0/219
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: 4, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding defined as fatal bleeding, symptomatic bleeding in a crucial area of organ, bleeding causing a reduction in haemoglobin concentration of >2g/dL or necessitating transfusion of > 2 units of whole blood or RBC cells. at 6 months; Group 1: 3/220, Group 2: 0/219
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN versus ENOXAPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Sudden, otherwise unexplained death (presumed to be a result of PE, acute myocardial infarction, or stroke). at 6 months; Group 1: 0/220, Group 2: 1/219
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT symptomatic only (not analysed) at 6 months; Group 1: 14/220, Group 2: 6/219
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE (symptomatic). Pulmonary embolism was identified by performing a high-probability lung scan; an intermediate-probability lung scan in the presence of objectively confirmed deep vein thrombosis; a diagnostic spiral computed tomography scan; diagnostic pulmonary angiography; or diagnostic transesophageal echocardiography. at 6 months; Group 1: 4/220, Group 2: 0/219
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding defined as fatal bleeding, symptomatic bleeding in a crucial area of organ, bleeding causing a reduction in haemoglobin concentration of >2g/dL or necessitating transfusion of > 2 units of whole blood or RBC cells. at 6 months; Group 1: 0/220, Group 2: 0/219
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Did not receive study drug because not treated with thalidomide; Group 2 Number missing: 2, Reason: Did not receive study drug because not treated with thalidomide

Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	**PRODIGE trial: Perry 2010[258]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=186)
Countries and setting	Conducted in Canada; Setting: 15 centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months + 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Stratified according to centre, tumor grade (3 and 4), the KPS scale (≤60 vs 70 or more), time from surgery to randomisation (<2 weeks vs 2-4 weeks)
Inclusion criteria	Patients with malignant glioma who had completed surgery and were receiving further treatment and ongoing care. 18 years and over, newly diagnosed, pathologically confirmed WHO Grade 3 or 4 glioma (anaplastic astrocytoma, glioblastoma multiforme, gliosarcoma, anaplastic oligodendroglioma or anaplastic mixed glioma)
Exclusion criteria	acute or chronic DVT demonstrated objectively, evidence of serious haemorrhage within 4 weeks of study entry, coagulopathy, symptomatic intracranial or intratumoral bleeding, acute peptic ulcer disease, familial bleeding diathesis, a requirment for long-term anticoagulants, an expected lifespan < 6 months and body weight <40kg, or pregnancy, of childbearing potential, not using adequate contraception, geographically inaccessible for follow-up, unable to commence study drug within 4 weeks of original surgery or biopsy.
Recruitment/selection of patients	Trial began October 2002. Recruitment was lower than anticipated and the study was closed to recruitment in May 2006 as a result of expiration of the study drug.
Age, gender and ethnicity	Age - Mean (range): Daltaparin: 57 (30-81), Placebo 55 (26-77) years. Gender (M:F): 111/75. Ethnicity: NR
Further population details	1. BMI : Not applicable 2. Chemotherapy: Not applicable (unclear what further post-surgical treatment was undertaken.). 3. Renal impairment: Not applicable 4. Tumour: Solid (Malignant glioma).
Extra comments	Pre/perioperative DVT prophylaxis (patients can be in more than one group):

	AES: dalt 48% placebo 46% UFH: dalt 18% placebo 8% LMWH: dalt 15% placebo 15% No prophylaxis: dalt 47% placebo 43%
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Low molecular weight heparin - Dalteparin. Dalteparin sodium 5000 IU administered subcutaneously once daily in prefilled syringes. Duration 6 months. Concurrent medication/care: Over half (53%) of patients received some other form of pre- or peri-operative DVT prophylaxis (AES or heparin or both). Use of concurrent acetylsalicyclic acid (ASA), NSAIDs and dextran was permitted but discouraged. 78% had radiotherapy within the first month. (n=87) Intervention 2: No treatment - Placebo. Saline placebo administered subcutaneously once daily in prefilled syringes. Duration 6 months. Mean duration 157 days. Concurrent medication/care: Over half (57%) of patients received some other form of pre- or peri-operative DVT prophylaxis (AES or heparin or both). Use of concurrent acetylsalicyclic acid (ASA), NSAIDs and dextran was permitted but discouraged. 90% had radiotherapy within the first month.
Funding	Study funded by industry (Funding and research support from Pfizer Inc, Ontario Clinical Oncology Group, Crolla Chair in Brain Tumor Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Overall mortality at 6 months; Group 1: 18/91, Group 2: 11/76
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 11

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: Symptomatic DVT only (not analysed) confirmed by venography or compression sonography at 6 months; Group 1: 8/91, Group 2: 10/76
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 11

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE confirmed by autopsy, a high probability ventilation-perfusion lung scan, conventional pulmonary angiogram at 6 months; Group 1: 2/91, Group 2: 4/76
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low,

Subgroups - Low, Other 1 - Low, Other 2 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 11 Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Clinically overt and satisfied one of: decrease in hemoglobin of 20mg/L or more over 48 hours, bleeding leading to transfusion of 2 or more units, retoperitoneal, intracranial, intraspinal, intraocular or pericardial bleeding, bleeding leading to an invasive intervention or death. at 6 months; Group 1: 3/91, Group 2: 0/76 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 11	
Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	**PROTECHT (Prophylaxis of Thromboembolism during Chemotherapy); ClinicalTrials.gov Identifier:NCT00951574 trial: Agnelli 2009[2]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1166)
Countries and setting	Conducted in Italy; Setting: 62 centres across Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): Recruitment was between October 2003 and May 2007. Median duration of follow-up was 111 and 113 days in the nadroparin and placebo groups respectively
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Ambulatory patients older than 18 years of age who were receiving chemotherapy for metastatic or locally advanced lung, gastrointestinal (stomach, colon, or rectum), pancreatic, breast, ovarian, or head and neck cancer.
Exclusion criteria	Patients on adjuvant or neoadjuvant chemotherapy; objectively confirmed venous or arterial thromboembolism in the past 3 months; antithrombotic treatment for any indication; life expectancy of less than 3 months; ECOG score of >2;

	active bleeding or bleeding requiring hospitalization or transfusion or surgical intervention in the past 4 weeks; intracranial bleeding in the past 6 months; high risk of bleeding (INR or activated partial thromboplastin time ratio above 1.3, or platelet count <50 X 10^9/L); known active or gastric or duodenal ulcer, known cerebral metastasis; severe and uncontrolled hypertension; renal impairment (creatinine concentration >0.025 mg/mL); substantial liver insufficiency; and known hypersensitivity to heparin and derivatives.
Recruitment/selection of patients	See inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): Nadroparin 62.1 (10.3); Placebo 63.7 (9.2). Gender (M:F): Nadroparin: 372:397; placebo: 183:198. Ethnicity: Not reported
Further population details	1. BMI: Not obese (BMI under 30 kg/m2) (Nadroparin 25.4 (4.4); Placebo 25.2 (4.2)). 2. Chemotherapy: Chemotherapy (For Nadroparin and placebo respectively (n), patients were on either pyrimidine analogues: 485 vs 258; platinum compounds: 432 vs 225; anthracyclines (and related): 109 vs 58; nitrogen mustard analogues: 38 vs 18; or monoclonal antibodies: 27 vs 11). 3. Renal impairment: Not applicable 4. Tumour: Solid (For Nadroparin and placebo respectively (n), metastatic or locally advanced lung: 199 vs 80; gastrointestinal: 272 vs 148 (stomach (58 vs 40), colon (156 vs 79), or rectum (58 vs 29)), pancreatic (36 vs 17), breast (110 vs 55), ovarian (96 vs 47), or head and neck cancer (19 vs 17); other cancers: 37 vs 17).
Extra comments	Proportion of people with a central venous catheter was 41.9% in the nadroparin group and 38.6% in the placebo group. ClinicalTrials.gov Identifier:NCT00951574
Indirectness of population	No indirectness: Population directly related to review population
Interventions	(n=779) Intervention 1: Low molecular weight heparin - Licensed in country other than UK. Drug: Nadroparin calcium Nadroparin calcium; Pre-filled syringes of 0.4 ml (3.800 anti-Xa IU), 1 subcutaneous injection/day (every 24 hours). Duration Study treatment was started on the same day as chemotherapy (the first cycle or a new course), and was given for the duration of chemotherapy or up to a maximum of 12 days (+ or - 10 days). If the duration of chemotherapy was <4 months, study treatment was given after the last cycle of chemotherapy for a period of time equal to the duration of the last cycle. Concurrent medication/care: Antiplatelet agents, oral anticoagulants, fibrinolytic agents, unfractionated heparin or LMWH other than nadroparin were not allowed during the study period. The administration of NSAIDs was allowed with caution if considered necessary, and was monitored closely. Paracetamol was recommended as the first step for analgesic or anti-inflammatory treatment. All concomitant therapies were fully reported in case-report forms along with their daily dosage, duration, and reason for administration. (n=387) Intervention 2: No treatment - Placebo. Placebo Comparator: saline solution Pre-filled syringes of 0.4 ml, 1 subcutaneous injection/day (every 24 hours). Duration Study treatment was started on the same day as chemotherapy (the first cycle or a new course), and was given for the duration of chemotherapy or up to a maximum of 12 days (+ or - 10 days). If the duration of chemotherapy was <4 months, study treatment was given after the last cycle of

	chemotherapy for a period of time equal to the duration of the last cycle. Concurrent medication/care: Antiplatelet agents, oral anticoagulants, fibrinolytic agents, unfractionated heparin or LMWH other than nadroparin were not allowed durign the study period. The administration of NSAIDs was allowed with caution if considered necessary, and was monitored closely. Parecetamol was recommended as the first step for analgesic or anti-inflammatory treatment. All concomitant therapies were fully reported in case-report forms along with their daily dosage, duration, and reason for administration.
Funding	Study funded by industry (Italfarmaco)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LICENSED IN COUNTRY OTHER THAN UK versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death at By end of study treatment; Group 1: 33/769, Group 2: 16/381
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 6

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT symptomatic of lower or upper limbs plus incidentally diagnosed asymptomatic events at Median duration of follow-up was 111 and 113 days for nadroparin and placebo groups respectively; Group 1: 14/496, Group 2: 12/270
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: 273, Reason: Withdraw consent (57), non-compliance (31), protocol deviation (11), lost to follow-up (12), adverse events (101), death (10), disease progression (18), best interest of patient (15), other (18); Group 2 Number missing: 111, Reason: Consent withdrawn (27), non-compliance (14), protocol deviation (6), lost to follow-up (5), adverse event (33), death (3), disease progression (12), best interest of the patient (4), other (7)

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: PE symptomatic at Median duration of follow-up was 111 and 113 days for nadroparin and placebo groups respectively; Group 1: 3/496, Group 2: 3/270
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome assessment method not reported therefore downgraded once for indirectness ; Group 1 Number missing: 273; Group 2 Number missing: 111

Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding (fatal or clinically overt and associated with a decrease in hemoglobin of at least 0.02 g/mL over 48 hours, or with transfusion of 2 or more units of whole blood or red cells, occurred in a critical organ, required invasive intervention). at until 48 hours after the last injection of study drug; Group 1: 5/496, Group 2: 0/270

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 10; Group 2 Number missing: 6	
Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	**TOPIC-1 trial: Haas 2012-1[131]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=353)
Countries and setting	Conducted in Multiple countries; Setting: 39 centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: First occurrence of objectively confirmed VTE during the 6 month treatment period to include symptomatic or asymptomatic DVT (proximal or distal) confirmed by venography and/or ultrasonography; symptomatic PE confirmed by CT ventilation–perfusion scintigraphy, or shown at autopsy; thrombosis of the jugular or subclavian veins confirmed by ultrasonography; and superficial thrombophlebitis (if heparin-based treatment was required).
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients with objectively proven, disseminated metastatic breast carcinoma, receiving first- or second-line chemotherapy
Exclusion criteria	Inflammatory breast cancer or were receiving anthracycline monotherapy or gemcitabine (monotherapy or in combination). Also for the following reasons: bedridden; previous VTE diagnosis; current heparin or oral anticoagulant therapy; long-term aspirin or other current antiplatelet drugs; active gastrointestinal bleeding; hemorrhagic stroke; hereditary bleeding disorder; thrombocytopenia (platelets <75 000/mL); partial thromboplastin time >2 X the upper limit of normal (ULN); osteoporotic fracture; myocardial infarction in the preceding 6 months; and participation in a clinical trial with an experimental drug in the preceding 4 weeks.

Recruitment/selection of patients	Patients were allocated to the lowest available randomization number available for each study centre. Randomization numbers were allocated sequentially as patients were enrolled at each centre
Age, gender and ethnicity	Age - Mean (SD): Certoparin: 54.6 (10.3); placebo: 56.6 (11.0). Gender (M:F): Unclear . Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) 2. Chemotherapy: Not applicable 3. Renal impairment: Not applicable 4. Tumour:
Extra comments	There was an extended time frame between diagnosis and study treatment initiation (mean 3.2 years). TOPIC-1 was terminated prematurely because the rate of VTE was substantially lower than anticipated, with few events - study was underpowered to detect a difference.
Indirectness of population	No indirectness
Interventions	(n=174) Intervention 1: Low molecular weight heparin - Licensed in country other than UK. Certoparin sodium (Mono Embolex, Novartis GmbH, Nurnberg, Germany) Study drug was supplied as a pre-filled 3-mL multidose pen - an injection volume of 0.3 mL containing 3000 IU certoparin, or isotonic saline administered once daily. Duration once daily for 6 months. Concurrent medication/care: First- or second-line chemotherapy (n=179) Intervention 2: No treatment - Placebo. No details given other than 'placebo'. Duration once daily for 6 months. Concurrent medication/care: First- or second-line chemotherapy for objectively proven, disseminated metastatic breast carcinoma
Funding	Study funded by industry (The TOPIC studies were supported by an unrestricted grant from Novartis Pharma GmbH, Germany. The investigators remained in control of the study database. Interpretation of data and preparation of the manuscript were undertaken by the investigators, and fulfilled a requirement within the protocol.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LICENSED IN COUNTRY OTHER THAN UK versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Overall mortality at 6 months; Group 1: 15/174, Group 2: 12/178
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: 1 not treated and 1 excluded (reasons not clear)

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT: first occurrence of objectively confirmed DVT during the 6-month treatment period to include symptomatic or asymptomatic DVT (proximal or distal) at 6 months; Group 1: 7/174, Group 2: 7/177
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 -

High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: 1 not treated and 1 excluded (reasons not clear) Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome: Symptomatic PE at 6 months; Group 1: 1/174, Group 2: 1/177 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: 1 not treated and 1 excluded (reasons not clear) Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Bleeding events - major bleeding at 6 months; Group 1: 3/174, Group 2: 0/177 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: 1 not treated and 1 excluded (reasons not clear) Protocol outcome 5: Heparin-induced thrombocytopenia at up to 90 days from hospital discharge - Actual outcome: Thrombocytopenia at 6 months; Group 1: 25/174, Group 2: 16/177 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: 1 not treated and 1 excluded (reasons not clear)	
Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	**TOPIC-2 trial: Haas 2012-2[131]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=547)
Countries and setting	Conducted in Multiple countries; Setting: 39 centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: First occurrence of objectively confirmed VTE during the 6 month treatment period to include symptomatic or asymptomatic DVT (proximal or distal) confirmed by venography and/or ultrasonography; symptomatic PE confirmed by CT ventilation–perfusion scintigraphy, or shown at autopsy; thrombosis of the jugular or subclavian veins confirmed by ultrasonography; and superficial thrombophlebitis (if heparin-based treatment was required).
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients with objectively proven, inoperable disseminated primary non–small cell lung carcinoma of stage III or IV receiving standard first- or second-line chemotherapy
Exclusion criteria	Patients were excluded from TOPIC-2 if they had small-cell lung carcinoma, brain metastases, hemoptysis of ≥ grade 2, or a Karnofsky index <70. Also for the following reasons: bedridden; previous VTE diagnosis; current heparin or oral anticoagulant therapy; long-term aspirin or other current antiplatelet drugs; active gastrointestinal bleeding; hemorrhagic stroke; hereditary bleeding disorder; thrombocytopenia (platelets <75 000/mL); partial thromboplastin time >2 X the upper limit of normal (ULN); osteoporotic fracture; myocardial infarction in the preceding 6 months; and participation in a clinical trial with an experimental drug in the preceding 4 weeks.
Age, gender and ethnicity	Age - Mean (SD): Certoparin: 60.8 (9.5); placebo: 60.3 (10.0). Gender (M:F): Certoparin: 227:46; placebo: 227:46. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) 2. Chemotherapy: Chemotherapy 3. Renal impairment: Not applicable 4. Tumour: Solid
Extra comments	The patients enrolled in TOPIC-2 were newly diagnosed with cancer, with a mean time between diagnosis and study treatment initiation of 0.3 years.
Indirectness of population	No indirectness
Interventions	(n=273) Intervention 1: Low molecular weight heparin - Licensed in country other than UK. Certoparin sodium (Mono Embolex, Novartis GmbH, Nurnberg, Germany) Study drug was supplied as a pre-filled 3-mL multidose pen - an injection volume of 0.3 mL containing 3000 IU certoparin, or isotonic saline administered once daily. Duration once daily for 6 months. Concurrent medication/care: receiving standard first- or second-line chemotherapy (n=274) Intervention 2: No treatment - Placebo. No details given other than 'placebo'. Duration once daily for 6 months. Concurrent medication/care: receiving standard first- or second-line chemotherapy
Funding	Study funded by industry (The TOPIC studies were supported by an unrestricted grant from Novartis Pharma GmbH, Germany. The investigators remained in control of the study database. Interpretation of data and preparation of the

	manuscript were undertaken by the investigators, and fulfilled a requirement within the protocol.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LICENSED IN COUNTRY OTHER THAN UK versus PLACEBO Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: Overall mortality at 6 months; Group 1: 55/273, Group 2: 59/273 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 excluded; Group 2 Number missing: 10, Reason: 1 not treated and 9 excluded Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT: first occurrence of objectively confirmed DVT during the 6-month treatment period to include symptomatic or asymptomatic DVT (proximal or distal) at 6 months at 6 months; Group 1: 12/268, Group 2: 22/264 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 excluded; Group 2 Number missing: 10, Reason: 1 not treated and 9 excluded Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome: Symptomatic PE at 6 months; Group 1: 2/268, Group 2: 4/264 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 excluded; Group 2 Number missing: 10, Reason: 1 not treated and 9 excluded Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Bleeding events - major bleeding at 6 months; Group 1: 10/273, Group 2: 6/273 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 excluded; Group 2 Number missing: 10, Reason: 1 not treated and 9 excluded Protocol outcome 5: Heparin-induced thrombocytopenia at up to 90 days from hospital discharge - Actual outcome: Thrombocytopenia at 6 months; Group 1: 74/273, Group 2: 86/273 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 excluded; Group 2 Number missing: 10, Reason: 1 not treated and 9 excluded	
Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

H.15 Patients with central venous catheters

Study	De Cicco 2009[79]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=450)
Countries and setting	Conducted in Greece, Italy
Line of therapy	Not applicable
Duration of study	Intervention time: 9-11 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	cancer patient; 18 years of age or over; life expectancy of at least 3 months; scheduled for CVC insertion for chemotherapy administration
Exclusion criteria	previous CVC insertion; known hypersensitivity to X-ray contrast; renal failure (serum creatinine level >180 lmol/l); active gastric peptic ulcer or severe hepatic disease; DVT in the previous 3 months or cerebral bleeding in the previous 6 months; known cerebral metastasis; bleeding disorders [activated partial thromboplastin time (aPTT) 30% longer than the control value and international normalized ratio (INR) > 1.5]; platelet count <80 · 109/l; antithrombin III <60%; treatment with unfractionated heparin, LMWH, oral anticoagulants or antiplatelet agents within 5 days before CVC insertion; pregnancy and refusal to give written consent
Recruitment/selection of patients	Consecutive cancer patients who met the inclusion criteria, from February 2000 to June 2004
Age, gender and ethnicity	Age - Mean (SD): 55 (12). Gender (M:F): 165:285. Ethnicity: not reported
Further population details	1. Active cancer: Active cancer 2. BMI : Not applicable (Weight, mean (SD): acenocoumarol 70.9 (13); dalteparin 68.6 (12.8); no treatment 71 (14.7)). 3. Renal impairment: Not applicable (not stated).
Extra comments	Cancer localisation: breast 32%; gastrointestinal 28%; hepatic or biliary tract 3.3%; pancreatic 2.5%; genitourinary 12.4%; hematologic 6.2%; head and neck 5.6%; lung 2%. Metastatic 56.4%
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Vitamin K antagonists - Acenocoumarol . Acenocoumarol 1mg/day for 3 days before and 8 days after CVC insertion. Duration 11 days. Concurrent medication/care: Chemotherapy (n=150) Intervention 2: Low molecular weight heparin - Dalteparin. Dalteparin 500IU, 2 hours before CVC insertion and daily after for 8 days. Duration 9 days. Concurrent medication/care: Chemotherapy

Study	De Cicco 2009[79]
	(n=150) Intervention 3: No treatment - No VTE prophylaxis treatment. No treatment. Duration 11 days. Concurrent medication/care: Chemotherapy
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACENOCOUMAROL versus DALTEPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Mortality at 30 days; Group 1: 14/114, Group 2: 12/120; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT, CVC-related (definition not reported) at 30 days; Group 1: 25/114, Group 2: 48/120; Risk of bias: High; Indirectness of outcome: Serious

Protocol outcome 3: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding (clinically overt bleeding associated with a decrease in haemoglobin level of at least 2d/dL or requiring a transfusion of 2 or more units of packed red cells in any 24 hour period) at 30 days; Group 1: 0/114, Group 2: 0/120; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACENOCOUMAROL versus NO VTE PROPHYLAXIS TREATMENT

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Mortality at 30 days; Group 1: 14/114, Group 2: 11/114; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT, CVC-related (definition not reported) at 30 days; Group 1: 25/114, Group 2: 60/114; Risk of bias: High; Indirectness of outcome: Serious

Protocol outcome 3: Major bleeding at up to 45 days from hospital discharge
- Actual outcome: Major bleeding (clinically overt bleeding associated with a decrease in haemoglobin level of at least 2d/dL or requiring a transfusion of 2 or more units of packed red cells in any 24 hour period)at 30 days; Group 1: 0/114, Group 2: 0/114; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN versus NO VTE PROPHYLAXIS TREATMENT

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Mortality at 30 days; Group 1: 12/120, Group 2: 11/114; Risk of bias: Very high; Indirectness of outcome: No indirectness

Study	De Cicco 2009[79]
Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT, CVC-related (definition not reported) at 30 days; Group 1: 48/120, Group 2: 60/114; Risk of bias: High; Indirectness of outcome: Serious Protocol outcome 3: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Mortality (clinically overt bleeding associated with a decrease in haemoglobin level of at least 2d/dL or requiring a transfusion of 2 or more units of packed red cells in any 24 hour period) at 30 days; Group 1: 0/120, Group 2: 0/114; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Pulmonary embolism at 90 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Karthaus et al., [170] Country of study: 48 centres from 12 countries Study design: RCT List who was masked to interventions: Patient, clinician and outcome assessor Evidence level:	Patient group: Patients with documented cancer with central venous catheter. Setting: Unclear Inclusion criteria: Patients with histologically confirmed malignancy; placement of a CVC for chemotherapy within 5-7 days prior to randomisation and treatment; expected length of catheter use of at least 12 weeks; age ≥ 18 years; weight ≥ 40kg; Eastern Cooperative Oncology Group performance status of 0,1 or 2; life expectancy of at least 16 weeks; adequate pre-treatment organ function as demonstrated by a platelet count of at least 100,000/mm3; absolute neutrophil count of at least 1500/mm3; total bilirubin and serum creatinine of up to 2 x the upper limit of normal; AST	Group 1 Low Molecular Weight Heparin (Dalteparin) Start time: unclear End time: unclear Duration: 16 weeks Dose and frequency: 5000IU injected subcutaneously once daily Group 2 Placebo	All-cause mortality	Group1: 4/285 Group 2: 1/140 P value: NS	Funding: Pfizer Limitations: 2:1 randomisation of dalteparin: placebo. Significantly more patients had solid tumours in the Dalteparin group. Outcomes not reported: Deep vein thrombosis, Heparin induced thrombocytopaenia, pulmonary hypertension, post thrombotic syndrome, Quality of life, length of stay
			Catheter related clinically relevant pulmonary embolism (confirmed by: ventilation perfusion scan or spiral CT scan)	Group1: 1/294 Group 2: 0/145 P value: NS	
			Clinically relevant catheter related thrombosis1 (screened for by: upper extremity evaluation by venography, ultrasound or computed tomography CT scan)	Group1: 10/294 Group 2: 5/145 P value: 0.980*	
			Asymptomatic catheter related thrombosis2 (confirmed by: upper extremity evaluation by venography, ultrasound or computed	Group1: 10/294 Group 2: 6/145 P value: 0.788*	

Study		De Cicco 2009[79]			
1+ Duration of follow-up: 16 weeks	up to 3 x (patients without liver metastasis) or 5 x (patients with liver metastasis) the upper limit of normal; a PT/aPTT up to 1.5 x the upper limit of normal. Exclusion criteria: known hypersensitivity to dalteparin; other LMWH or unfractionated heparin; active gastrointestinal or genitourinary tract bleeding; known coagulopathy; requirement for aspirin, dipyridamole, UFH, other LMWHs, warfarin or other anticoagulation therapy; active uncontrolled infection, including suspected catheter related infection,; known HIV positivity or AIDS related illness; eye, ear or NS surgery or a CNS trauma within the last 3 months; intracranial or intraocular haemorrhage (within1 year) or retinal detachment (within 6 months); mental incapacitation or psychiatric illness that would prevent the provision of informed consent; uncontrolled cardiac arrhythmia; severe concurrent disease; leukaemia requiring induction/consolidation chemotherapy during the 16 study week period; requirement of high dose chemotherapy and stem cell transplantation during the 16 week study period; use of investigational or unapproved catheter devices; and pregnancy, breastfeeding or likelihood of pregnancy.	Start time: Unclear End time: Unclear Duration: 16 weeks Dose and frequency: 0.2ml saline solution Additional non-comparative prophylaxis: Catheter flushing with unfractionated heparin (500IU)/saline boluses were allowed during catheter use.	tomography CT scan)		Additional outcomes reported: Catheter related infection, non-catheter related arterial or venous thromboembolic events Notes: * Calculated by the NCC team using Fisher exact test. Catheter related thrombosis Clinically relevant catheter related thrombosis = thrombosis that was symptomatic or that required anticoagulant therapy or therapeutic infusion of a fibrinolytic agent with or without catheter removal Asymptomatic catheter thrombosis = not requiring any intervention.
			Major bleeding (description: as described by adjudication committee)	Group1: 1/294 Group 2: 1/145 P value: 0.522*	
			All bleeding (Table of all recorded bleeding (including location of bleed) is provided as table 5 in the paper)	Group1: 50/285 Group 2: 21/140 P value: 0.581*	

Study	De Cicco 2009[79]				
	All patients N: 439 Age (mean): Gp 1 Gp2 Mean ± SD 55.2±12.91 57.4 ±12.72 M/F (% female): 59.2 57.2 Additional risk factors: Gp1 Gp2 Weight mean (kg) ± SD 71.41±15.41 70.73±14.28 % Caucasian 94.6 93.8 Solid: Haematological tumours 271:23 125:20 Haematological Group 1 No. randomised: 294 No. of dropouts: 9 patients did not receive 1 dose 94 patients withdrew early from the study (reasons provided) Group 2 No. randomised: 145 No. of dropouts: 9 patients did not receive 1 dose 94 patients withdrew early from the study (reasons provided)				
Study	**Lavau-denes 2013[198]**				

Study	De Cicco 2009[79]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=420)
Countries and setting	Conducted in France; Setting: centre hospitalier universitaire de Limoges
Line of therapy	Not applicable
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	historical evidence of solid invasive cancer, locally advanced or metastatic status; presence of a subclavian central venous catheter inserted for less than 7 days; starting a first line of chemotherapy; aged 18 years or over; life expectancy of more than 3 months; performance status between 0 and 2 (ambulatory); platelets greater than 100 x 10^9/l and normal activated partial thromboplastin time (aPTT); capacity to provide informed consent
Exclusion criteria	renal or hepatic failure (creatinine clearance <20 ml/min); acute infectious disease; history of an allergic reaction to warfarin or heparin; uncontrolled blood pressure; ongoing haemorrhagic syndrome; concomitant disease which recommended heparin treatment; formal indication for warfarin or antiplatelets agents in preventative or curative doses; pregnant or breastfeeding woman; recent history of DVT in past 6 months; presence of cerebral metastasis; previous central venous access devices in past year
Recruitment/selection of patients	Consecutive patients enrolled from September 1999 to June 2009
Age, gender and ethnicity	Age - Mean (range): Control 60 (21-85); warfarin 59 (24-81); LMWH 61. Gender (M:F): 243:164. Ethnicity: not reported
Further population details	1. Active cancer: Active cancer (historical evidence of solid invasive cancer, locally advanced or metastatic status). 2. BMI : Mixed (<35 97.3%; ≥35 2.2%). 3. Renal impairment: No renal impairment (eGFR greater than 45 ml/min/1.73 m^2) (excluded people with renal failure).
Extra comments	Primary cancer location: head and neck 23.6; breast 10.6; lung or pleura 11%; colorectal and anal 14.7%; oesophagus and stomach 15.7%; pancreas and biliary tract 5%; urinary (kidney and tract) 7.9%; pelvic gynaecological 4.7%. Previous surgery 25.8%
Indirectness of population	No indirectness
Interventions	(n=141) Intervention 1: Low molecular weight heparin - Mixed. Subcutaneous LMWH (dalteparine, nadroparine or enoxaprine) at recommended doses for prevention, once daily. Doses were not adjusted. Treatment started in the first 6 days after central venous access device implementation. Duration 90 days. Concurrent medication/care: chemotherapy

Study	De Cicco 2009[79]
	(n=137) Intervention 3: No treatment - No VTE prophylaxis treatment. No prophylaxis. Duration 90 days. Concurrent medication/care: chemotherapy
Funding	Other (Clinical Research and Innovation of Limoges Hospital)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LMWH versus NO VTE PROPHYLAXIS TREATMENT

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Mortality at 90 days; Group 1: 0/138, Group 2: 0/135; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT, catheter-related (confirmed by Doppler US and venograpy) at 90 days; Group 1: 14/138, Group 2: 8/134; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: DVT, non-catheter-related (confirmed by Doppler US and venograpy) at 90 days; Group 1: 1/138, Group 2: 7/135; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Pulmonary embolism (definition not reported) at 7-90 days from hospital discharge
- Actual outcome: PE with no etiological DVT at 90 days; Group 1: 0/138, Group 2: 1/135; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism at 90 days from hospital discharge; Major bleeding at up to 45 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Monreal et al., 1996457 Country of study: Spain Study design: RCT	Patient group: Cancer patients with central venous catheters Setting: Unclear Inclusion criteria: all cancer patients	Group 1 LMWH (Fragmin) Start time: 2 hours before insertion of the catheter Duration: 90 days or until there was	All-cause mortality Mortality from cancer progression	Group1: 1/17 Group 2: 2/15 P value: 0.589*	Funding: No information is provided regarding funding. Limitations: No information about randomisation
			Asymptomatic subclavian DVT (confirmed by: Venography) Paper reports that 8/9	Group1: 1/16 Group 2: 8/13 P value: 0.003*	

Study		De Cicco 2009[79]			
List who was masked to interventions: Venogram interpreters. Evidence level: 1+ Duration of follow-up: 90 days	who underwent placement of a long term Port-a-Cath subclavian venous catheter and had projected survivals of over 3 months. Exclusion criteria: Patients who had baseline platelet counts under 100x109/l, previous subclavian vein catheters, obstructing mediastinal tumours, previous history of DVT, or anatomic lesions that bleed. All patients N: 32 Age (mean): 54 (range 27 – 77) M/F: 17:15 Additional risk factors: Cancer location Gp1 Gp2 Colon 8 7 Breast 4 2 Sarcoma 2 1 Mesothelioma 1 2 Stomach 1 1 Metastases Gp1 Gp2 Liver 6 7 Lung 5 4 Bone 2 1 Brain 1 1 Others 2 1	venographic evidence of thrombosis. Dose, and frequency: 2500IU subcutaneously once daily. Group 2 No prophylaxis Additional non-comparative prophylaxis: None mentioned	events were symptomatic but does not provide details of which group they occurred in. Major bleeding (description: haematoma requiring surgical intervention)	 Group1: 1/16 Group 2: 0/12 P value: NS	method, allocation concealment in the paper. The paper does not state whether patients or clinicians were blind to treatment allocation. Outcomes not reported: Pulmonary embolism, lower extremity DVT, Fatal, neurological or minor bleeding, post thrombotic syndrome, pulmonary hypertension, heparin induced thrombocytopaenia, quality of life, length of stay. Additional outcomes reported: Infection Notes: * Calculated by NCC using Fisher exact tests.

Study	De Cicco 2009[79]				
	Gp1 Gp2 Infection 0 1 Group 1 No. randomised: 17 No. of dropouts: 1 died Group 2 No. randomised: 15 No. of dropouts: 2 died				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Niers et al., 2007489 Country of study: The Netherlands Study design: RCT List who was masked to interventions: Patient, healthcare	Patient group: Patients with haematologic malignancies requiring central venous catheters, Setting: Unclear Inclusion criteria: Consecutive patients with haematologic malignancies who were going to receive a CVC for high-dose chemotherapy including autologous stem cell transplantation.	Group 1 Low Molecular Weight Heparin Nandoparin (Fraxiparin) Start time: 2hr before CVC insertion End time: 3 weeks or until day of catheter removal whichever came first Dose, and	Symptomatic catheter related central venous thrombosis (confirmed by: venography)	Group1: 0/41 Group 2: 1/46 P value: NS	Funding: Paper states that the study drug was obtained commercially and there was 'financial support' for the study. No further details were provided. Limitations: No information about method of randomisation and allocation
			Catheter related central venous thrombosis (confirmed by: ultrasound confirmed by venography)	Group1: 7/41 Group 2: 4/46 P value: 0.336*	
			Major bleeding (description: overt bleeding with a fall in haemoglobin of 2g/dL or more, or leading to a transfusion of 2 or more units of packed red	Group1: 0/56 Group 2:0/57 P value: NS	

professionals and investigators assessing outcome Evidence level: 1+ Duration of follow-up: 3 weeks	Exclusion criteria: Patients aged less than 17 years allergy to i.v. contrast medium, previous catheter related CVT, current use or indication for anticoagulant treatment acute promyelocytic leukaemia Previous CVC Evident haemorrhagic diathesis Renal failure (creatinine >200 µmol/L) All patients N: 202 eligible, 113 randomised Reasons for non-randomisation given Age : Gp1 Gp2 mean ± SD 58±10 53±13 M/F: 62:51 Additional risk factors: Haematologic tumours Gp1 Gp2 Acute myeloid leukaemia 23 17 Multiple lymphoblastic leukaemia 2 10 Multiple myeloma 14 16 (Non)-Hodgkin lymphoma – relapsed 17 14	frequency: 2850 antifactor Xa (antiFXa) units subcutaneously once daily Group 2 Placebo (no details provided) Dose and frequency: subcutaneous injections once daily Additional non-comparative prophylaxis: None indicated in the paper.	blood cells or bleeding in a critical organ such as intracranial, retroperitoneal or pericardial bleeding, or contributing to death.)		concealment. 24% of randomised patients did not complete the study Outcomes not reported: Pulmonary Embolism, Lower limb DVT, pulmonary hypertension, post thrombotic syndrome, quality of life, length of stay, all-cause mortality. Additional outcomes reported: Catheter related infection Notes: CVT – central venous thrombosis CVC – central venous catheter *Calculated by the NCC using Fisher Exact Test
			Clinically relevant non-major bleeding (description: overt bleeding not meeting the criteria for major bleeding, and included skin haematoma if the size was larger than 100 cm^2, epistaxis lasting for more than 5 minutes or repetitive or leading to an intervention, macroscopic haematuria if spontaneous or lasting for more than 24 hours after instrumentation or any other bleeding type that was considered to have clinical consequences for the patient.)	Group1: 2/56 Group 2: 2/57 P value: NS	
			Minor bleeding (description: all other bleeding episodes not meeting the criteria for clinically relevant non-major bleeding)	Group1:5/56 Group 2: 2/57 P value: 0.271*	

	Group 1 No. randomised: 56 No. of dropouts: 15 (27%) Group 2 No. randomised: 57 No. of dropouts: 11 (19%)		Heparin induced thrombocytopaenia (description: clinical suspicion and positive antibodies against the heparin-platelet FIV complex)	Group1: 0/56 Group 2: 0/57 P value: NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Verso et al., 2005663 Country of study: Italy Study design: RCT List who was masked to interventions: Patients, healthcare professionals and investigators assessing VTE end points	Patient group: Cancer patients with a central venous catheter Setting: Unclear Inclusion criteria: Consecutive patients aged 18 years or older who were scheduled for CVC insertion for chemotherapy if they had a life expectance of at least 3 months and adequate venous access to perform venography of the upper limb and if the CVC was to be left in site for longer than 6 weeks. Exclusion criteria: Renal failure (serum creatinine >2.0 mg/dL)	Group 1 Low Molecular Weight Heparin - Enoxaparin (Clexane) Start time: 2 hours prior to CVC insertion Duration: 42 days ±2 days Dose, and frequency: 40mg injection subcutaneously once per day. Group 2 Placebo	All-cause mortality	After treatment Group1: 5/191 Group 2: 2/194 P value: 0.281* After follow up (3 months) Group1: 13/191 Group 2: 20/194 P value: 0.2875*	Funding: Supported by a grant from Aventis Pharmaceuticals. Limitations: The paper states that randomisation was completed using 'random numbers' but no indication of how these were generated. No information about allocation concealment. Outcomes not reported:
			Fatal pulmonary embolism (confirmed by: autopsy)	Group1: 0/191 Group 2: 0/194 P value: NS	
			Symptomatic upper limb DVT (confirmed by: venography)	Group1: 2/155 Group 2: 6/155 P value: 0.283*	
			asymptomatic or symptomatic upper limb DVT (confirmed by: venography)	Group1: 22/155 Group 2: 28/155 P value: 0.44*	

Evidence level: 1+ Duration of follow-up: 3 months	Known hypersensitivity to x-ray contrast medium Previous CVC insertion on the ipsilateral side Cerebral thrombosis or bleeding in the previous 6 months or known cerebral metastasis Bleeding disorders (APTT and/or prothrombin time 30% longer than control values) or platelet count less than 80 x 109/L Active gastric peptic ulcer or severe hepatic disease Uncontrolled arterial hypertension Known hypersensitivity to unfractionated heparin or LMWHs Objectively confirmed DVT within the previous 3 months Treatment with heparin, LMWH, oral anticoagulants or antiplatelet agents within 5 days before CVC insertion Pregnancy Anticipated inability to participate in the study for 3 months Patients with CVC for parenteral nutrition only All patients N: 385 Age: Gp 1 Gp2 Mean±SD 59.1±11.9 59.5±12.4 M/F: 176:209 Additional risk factors:	Start time: 2 hours prior to CVC insertion Duration: 42 days ±2 days Additional non-comparative prophylaxis: Paper states treatment with aspirin, antiplatelet agents or nonsteroidal anti-inflammatory agents were not allowed during the trial.	Major bleeding (description: decrease in haemoglobin level of at least 2g/dL or requiring a transfusion of two or more units of packed red cells. Intracranial, retroperitoneal, and intraocular bleeding and bleeding requiring surgical intervention)	Group1: 0/191 Group 2: 0/194 P value: NS	Lower limb DVT, Pulmonary Embolism, Neurological bleeding, Upper GI bleeding, Heparin induced thrombocytopaenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay Additional outcomes reported: Thrombocytopaenia Notes: * calculated by NCC team using Fisher Exact Test
			Minor bleeding (description: All other bleeding)	Group1: 12/191 Group 2: 7/194 P value: 0.248*	

	Cancer Localisation Gp1 Gp2 Gastrointestinal 100 108 Hepatic or biliary tract 0 7 Pancreatic 3 6 Genitourinary 14 10 Lung 4 3 Head and neck 13 6 Breast 34 34 Haematological 16 17 Skin 1 2 Other 7 3 Unknown 2 2 Cancer Histology Gp1 Gp2 Adenocarcinoma 157 162 Lymphoma and leukaemia 13 14 Sarcoma 4 2 Other 15 11 Unknown 1 4 Cancer stage Gp1 Gp2 Metastatic 145 139 Non metastatic 41 45 Unknown 4 4 Surgery, No of patients Gp1 Gp2 Previous ≤3 months 83 79 Recent <3 months 72 68 Planned 3 4 Unknown 32 41				

	Chemotherapy Gp1 Gp2 Before CVC insertion 88 75 After CVC insertion 102 118 One agent 45 34 ≥2 agents 145 159 Other risk factors Gp1 Gp2 Axillary node dissection 27 28 Previous CVC of upper limb 16 23 Previous chest surgery 17 11 History of radiation to chest wall 15 12 History of previous VTE (<3months) 1 0 Axillary node involvement 11 6 Compression of superior vena cava 3 5 Family history of VTE 2 4 Oestrogen containing medications 1 1 Upper limb immobilisation 0 1 Group 1 No. randomised: 191 No. of dropouts: 36 (18.8%)				

	Group 2 No. randomised: 194 No. of dropouts: 39 (20.1)				

H.16 Palliative care

No relevant studies were identified.

H.17 Critical care

Study	**Cook 2011 [PROTECT]** [72]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3764)
Countries and setting	Conducted in Australia, Brazil, Canada, Saudi Arabia, United Kingdom, USA; Setting: 67 ICUs in academic and community hospitals in the 6 countries.
Line of therapy	Prevention
Duration of study	Intervention time: Duration of stay in ICU
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was diagnosed on the first screening ultrasonography as prevalent DVT, reflecting a baseline characteristic. PE defined as definite (characteristic intraluminal filling defect on computed tomography of the chest, a high-probability ventilation ventilation-perfusion scan, or autopsy finding), probable (high clinical suspicion and either no test results or non-diagnostic results on noninvasive testing), or absent (negative or normal test results without reference to pretest probability). Major bleeding was defined as haemorrhage occurring at a critical site (e.g. intracranial haemorrhage), resulting in the need for a major therapeutic intervention (e.g. surgery), causing hemodynamic compromise, requiring at least 2 units of red-cell concentrates, or resulting in death.
Stratum	People who are not contraindicated for prophylaxis
Subgroup analysis within study	Not applicable
Inclusion criteria	Enrolled patients who were at least 18 years of age, weighed at least 45 kg, and were expected to remain in the ICU for at least 3 days.
Exclusion criteria	Major trauma, neurosurgery or orthopaedic surgery, need for therapeutic anticoagulant, heparin administration in the

	ICU for at least 3 days, contraindication to heparin or blood products, pregnancy, life support limitation, or enrollment in a related trial
Recruitment/selection of patients	Recruitment began in May 2006 and was completed in 4 years.
Age, gender and ethnicity	Age - Mean (range): 44.6-78.1. Gender (M:F): 1.32:1. Ethnicity: Not reported
Further population details	1. Active cancer: Mixed (History of cancer: Dalteparin group 4.4%; UFH group 3.7%). 2. BMI: Not obese (BMI under 30 kg/m2) (BMI: Dalteparin group 28.3±8.1, UFH group 28.2±7.3). 3. Renal impairment: Not applicable 4. Surgical/medical: Medical 5. Trauma: Not applicable
Extra comments	Diagnosis on admission (n for dalteparin = 1865, n for UFH= 1862): Cardiovascular condition - Dalteparin 8.9%, UFH 9.1%, Respiratory condition - Dalteparin 45.8%, UFH 45.4%, Gastrointestinal condition - Dalteparin 14.2%, UFH 13.7%, Renal condition - Dalteparin 2.1%, UFH 1.3%, Neurologic condition - Dalteparin 6.2%, UFH 6.1%, Sepsis - Dalteparin 14.6%, UFH 14.9%, Metabolic condition - Dalteparin 3.9%, UFH 3.8%. Length of stay: Dalteparin 9 (6-15), UFH 9 (6-16); Personal history of VTE (n for dalteparin = 1865; n for UFH = 1862) - Dalteparin 3.2%, UFH 3.2%. Family history of VTE - Dalteparin 1.4%, UFH - 1.6%. Central venous catheterisation (n for dalteparin and UFH= 1862) - Dalteparin 82.9%, UFH 84.9%. History of cancer (n for dalteparin = 1865; n for UFH = 1862) - Dalteparin 4.4$, UFH 3.7%
Indirectness of population	No indirectness
Interventions	(n=1873) Intervention 1: Low molecular weight heparin - Dalteparin. Subcutaneous dalteparin at a dose of 5000 IU once daily. Research pharmacists prepared identical syringes for subcutaneous injection of either dalteparin once daily plus placebo once daily. Duration of the ICU stay. Concurrent medication/care: N/A (n=1873) Intervention 2: Unfractionated heparin - low dose, administered subcutaneously. Subcutaneous unfractionated heparin at a dose of 5000 IU twice daily. Duration of ICU stay. Concurrent medication/care: N/A
Funding	Academic or government funding (Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada and the Australian and New Zealand College of Anesthetists Research Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN versus UNFRACTIONATED HEPARIN (UFH)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Mortality (in ICU) at up to 100 days; Group 1: 284/1873, Group 2: 304/1873; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic at 7-90 days from hospital discharge

- Actual outcome: Any DVT at time of death, discharge or at 100 days if patients were still hospitalized (Baseline screening for DVT was diagnosed using ultrasonography. The assumption was made that ultrasonography was also used to detect DVT at the reported time points); Group 1: 138/1873, Group 2: 161/1873; Risk of bias: High; Indirectness of outcome: No indirectness -Actual outcome: Proximal DVT at time of death, discharge or at 100 days if patients were still hospitalized (Baseline screening for DVT was diagnosed using ultrasonography. The assumption was made that ultrasonography was also used to detect DVT at the reported time points); Group 1: 96/1873, Group 2: 109/1873 Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome: PE at time of death, discharge or at 100 days if patients were still hospitalized (defined as characteristic intraluminal filling defect on computed tomography of the chest, a high probability ventilation-perfusion scan, or autopsy finding); Group 1: 18/1873, Group 2: 28/1873; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Major bleeding at up to 45 days from hospital discharge - Actual outcome: Major bleeding at time of death, discharge or at 100 days if patients were still hospitalized (defined as haemorrhage occurring at a critical site, e.g. intracranial haemorrhage, resulting in the need for a major therapeutic intervention, e.g. surgery, causing hemodynamic compromise, requiring at least 2 units of red-cell concentrates, or resulting in death); Group 1: 103/1873, Group 2: 105/1873; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Heparin-induced thrombocytopenia at up to 90 days from hospital discharge - Actual outcome: Heparin-induced thrombocytopenia at time of death, discharge or at 100 days if patients were still hospitalized (definition not reported); Group 1: 5/1873, Group 2: 12/1873; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Venous thromboembolism at up to 90 days from hospital discharge (definition not reported) -Actual outcome: VTE at time of death, discharge or at 100 days if patients were still hospitalised; Group 1: 154/1873, Group 2: 186/1873	
Protocol outcomes not reported by the study	Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge; Line associated thrombosis at duration of study

Study	**Vignon 2013** [329]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=406)
Countries and setting	Conducted in France; Setting: Nine ICUs in France
Line of therapy	Prevention

Duration of study	Intervention time: 6 days
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: DVT and PE - confirmation with compression ultrasonography (CUS)
Stratum	People who are contraindicated for pharmacological prophylaxis
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18 years or older who were at high risk of bleeding on ICU admission were eligible for the trial. High risk of bleeding was defined as symptomatic bleeding or the presence of organic lesions likely to bleed, hemophilic diseases, hemostatic abnormalities (platelet count <50,000/mm3, aPTT ratio >2, prothrombin time <40% or the presence of severe anaemia (haemoglobin <7 g/dl) due to bleeding or unexplained. (Patients contraindicated to pharmacological prophylaxis)
Exclusion criteria	Patient refusal, the absence of a high risk of bleeding, the presence of a documented VTE at screening or a recent DVT (<3 months), ICU stay of more than 36 hours or likely to be <72 hour, a life-support limitation, a contraindication for mechanical prophylaxis (i.e. severe lower limb arteriopathy, any arterial graft of the legs, a wound in the lower limb related to either vascular disease or trauma), and the presence of a mechanical prosthetic heart valve.
Recruitment/selection of patients	Between 21st November 2007 and 20th December 2010, a total of 407 patients underwent randomisation
Age, gender and ethnicity	Age - Mean (SD): 55.4 (17) years. Gender (M:F): 1.96:1. Ethnicity: Not reported
Further population details	1. Active cancer: Active cancer (IPC + AES group - 13.2%, AES group 12.4%). 2. BMI: Not obese (BMI under 30 kg/m2) (IPC + AES - 25.6±4.9, AES group BMI - 25.4±5.5). 3. Renal impairment: Not applicable 4. Surgical/medical: Not applicable 5. Trauma: Not applicable
Extra comments	Primary admission diagnostic category (%) - spontaneous intracranial haemorrhage 36%, traumatic intracranial haemorrhage 21.4%, multisystem trauma 10.8%, other haemorrhage 9.9%, severe sepsis or septic shock 9.6%, acute respiratory distress syndrome 5.9%, other diagnoses 6.4%; . Hospitalisation more than 48h prior ICU admission - 68%; Therapeutic anticoagulation - 7.1%; Thromboprophylaxis - 7.1%; Previous VTE- 3%; Cancer - 12.8%; Recent surgery or trauma - 29.1%; Pregnancy or post-partum - 1%; Oestrogren use - 1.5%; Known thrombophilia - 0.5%; Plaster cast immobilisation - 0%; Previous stroke - 3.2%; Cardiac insufficiency - 15.8%
Indirectness of population	No indirectness
Interventions	(n=202) Intervention 1: Anti-embolism stockings – AES only. AES consisted of thigh-length AES. Nurses were trained in the use of mechanical devices to apply optimal compression (proper sizing of AES and their proper application). AES was applied to both legs as soon as possible after randomisation and maintained continuously until compression ultrasonography (CUS) was performed on day 6. Duration 6 days. Concurrent medication/care: AES provided from T.E.D. anti-embolism stockings; Covidien, Mansfield. Anticoagulation was not permitted during the first 6 days of the study. The AES removal date and reasons were record when applicable. The use of AES was recorded to monitor compliance

	and tolerance. Compliance was considered poor if the mechanical devices were used less than 80% of the time. (n=205) Intervention 2: IPC + AES. IPC was achieved with using a compression system with adapted tubing sets and thigh sleeves. Nurses were trained in the use of mechanical devices to apply optimal compression (proper sizing of AES and IPC sleeves and their proper application). IPC and AES was applied to both legs as soon as possible after randomisation and maintained continuously until compression ultrasonography (CUS) was performed on day 6. Duration 6 days. Concurrent medication/care: IPC was SCD EXPRESS compression system and thigh sleeve was Covidien, Mansfield. Anticoagulation was not permitted during the first 6 days of the study. After that day, the decision to maintain VTE prophylaxis and its modality were left at the discretion of the investigators. The IPC and AES removal date and reasons were record when applicable. The use of IPC and AES was recorded to monitor compliance and tolerance. Compliance was considered poor if the mechanical devices were used less than 80% of the time.
Funding	Academic or government funding (Grant from the French Ministry of Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERMITTENT PNEUMATIC COMPRESSION (IPC) + AES versus ANTI-EMBOLISM STOCKINGS (AES) ONLY

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 6 days (assessed using compression ultrasonography); Group 1: 10/179, Group 2: 16/183; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Symptomatic DVT at 6 days (assessed using compression ultrasonography); Group 1: 0/204, Group 2: 0/202
- Actual outcome: Asymptomatic distal DVT (assessed using compression ultrasonography); Group 1: 6/179, Group 2: 12/183
- Actual outcome: Asymptomatic proximal DVT (assessed using compression ultrasonography); Group 1: 4/179 , Group 2: 4/183

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome: Symptomatic PE at 6 days (assessed using compression ultrasonography); Group 1: 0/205, Group 2: 1/202; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Fatal PE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 6 days (assessed using compression ultrasonography); Group 1: 0/204, Group 2: 0/202; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Venous thromboembolism (definition not reported)
- Actual outcome: VTE (symptomatic and asymptomatic) at 90 days; Group 1: 14/179, Group 2: 17/184

Protocol outcomes not reported by the study	Major bleeding at up to 45 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge; Line associated thrombosis at duration of study

H.18 Pregnant women and women up to 6 weeks postpartum

Study	**Burrows 2001[37]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=76)
Countries and setting	Conducted in Australia; Setting: Obstetric unit
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage)
Subgroup analysis within study	Not applicable
Inclusion criteria	Women having either elective or emergency caesarean section
Exclusion criteria	History of bleeding disorder, need of therapy with anticoagulation, history of thrombotic event, sensitivity to heparin, recent (3 months) history of GI haemorrhage or peptic ulcer, hepatic encephalopathy, renal dysfunction requiring dialysis, uncontrolled hypertension (systolic >200mmHG, diastolic >110mmHg), refusal to give informed consent, insufficient command of English to provide consent
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 31.7 (4.8), control group: 31.3 (5.5). Gender (M:F): Female. Ethnicity: Not reported
Further population details	1. Assisted conception: Non-assisted conception 2. BMI : Not applicable 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (5,000 daily; min 1,250 units daily - max 10,000 units daily). 2500U dalteparin. The first dose was administered no sooner than 4 hours postoperatively and no later than 24 hours postoperatively. Treatment packs contained enough syringes for 5 days of treatment.

	Duration 5 days. Concurrent medication/care: There were no restrictions on pain medication (n=37) Intervention 2: No treatment - Placebo. Placebo (saline). Duration 5 days. Concurrent medication/care: No restrictions on pain medication
Funding	Equipment / drugs provided by industry (Dalteparin and saline placebo provided by Phamacia and Upjohn)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (5,000 DAILY; MIN 1,250 UNITS DAILY - MAX 10,000 UNITS DAILY) versus PLACEBO

Protocol outcome 1: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at inpatients and up to 90 days from hospital discharge
- Actual outcome for Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage) : PE at 6 weeks; Group 1: 0/39, Group 2: 0/37
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death (including foetal death); occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (including adverse event for the foetus) at inpatient and up to 45 days from hospital discharge
- Actual outcome for Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage) : Major bleeding at 6 weeks; Group 1: 0/39, Group 2: 1/37
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: DVT (symptomatic) at 7-90 days from hospital discharge
- Actual outcome for Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage) : DVT at 6 weeks; Group 1: 1/39, Group 2: 0/37
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at inpatients and up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at inpatients and up to up to 90 days from

	hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy (including the foetus) at inpatients and up to up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Cruz 2011[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=646)
Countries and setting	Conducted in Spain; Setting: University hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage)
Subgroup analysis within study	Not applicable
Inclusion criteria	Women with a caesarean delivery who had not required prophylaxis or treatment with any type of LMWH during pregnancy and absence of allergy to heparin or derivatives
Exclusion criteria	Women who did not fulfil the duration of proposed prevention
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 31 (5.47). Gender (M:F): Female. Ethnicity: Not reported
Further population details	1. Assisted conception: Not applicable 2. BMI : Mixed (39.9% BMI>30, 9% BMI>35). 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=335) Intervention 1: Low molecular weight heparin (not licensed in UK) - Bemiparin (2500 units once daily - 3500 units once daily). 3500U once daily, post caesarean. Administered at least 8 hours following caesarean. Duration 10 days. Concurrent medication/care: Not reported (n=311) Intervention 2: Low molecular weight heparin (not licensed in UK) - Bemiparin (2500 units once daily - 3500 units once daily). 3500U once daily, post caesarean. Administered at least 8 hours following caesarean. Duration 5 days. Concurrent medication/care: Not reported
Funding	Study funded by industry (Supported by a research grant from the Laboratorios Fcos. ROVI, SA)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEMIPARIN (2500 UNITS ONCE DAILY - 3500 UNITS ONCE DAILY) - EXTENDED versus BEMIPARIN (2500 UNITS ONCE DAILY - 3500 UNITS ONCE DAILY) - STANDARD	

Protocol outcome 1: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at inpatients and up to 90 days from hospital discharge - Actual outcome for Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage) : PE at 3 months; Group 1: 0/335, Group 2: 0/311 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0 Protocol outcome 2: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome for Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage) : DVT at 3 months; Group 1: 0/335, Group 2: 0/311 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at inpatients and up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death (including foetal death); occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (including adverse event for the foetus) at inpatient and up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at inpatients and up to up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy (including the foetus) at inpatients and up to up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Heilmann 2007[143]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Germany; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with uncomplicated pregnancy and without risk factors for thrombosis
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 28 (6), UFH: 29 (5), AES: 28 (3). Gender (M:F): Female. Ethnicity: Not reported
Further population details	1. Assisted conception: Not applicable 2. BMI : Not obese (BMI under 30 kg/m2) (1.3% BMI >26). 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (5,000 daily; min 1,250 units daily - max 10,000 units daily). Dalteparin 5000U/daily during 7 days postoperatively. Duration 7 days. Concurrent medication/care: Not reported (n=50) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously; 15,000 units daily; third trimester increase to 20,000 units daily). 2x5000U UFH daily for 7 days postoperatively. The first dose was administered 6 hours following caesarean,. Duration 7 days. Concurrent medication/care: Not reported (n=50) Intervention 3: Anti-embolism stockings - Mixed above/below knee. AES were worn according to the guidelines of RCOG during hospital stays. Duration Not reported. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (5,000 DAILY; MIN 1,250 UNITS DAILY - MAX 10,000 UNITS DAILY) versus

UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY; 15,000 UNITS DAILY; THIRD TRIMESTER INCREASE TO 20,000 UNITS DAILY) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at inpatients and up to 90 days from hospital discharge - Actual outcome for Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage) : DVT at Up to hospital discharge; Group 1: 0/50, Group 2: 1/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 0 ; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (5,000 DAILY; MIN 1,250 UNITS DAILY - MAX 10,000 UNITS DAILY) versus MIXED ABOVE/BELOW KNEE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at inpatients and up to 90 days from hospital discharge - Actual outcome for Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage) : DVT at Up to hospital discharge; Group 1: 0/50, Group 2: 1/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 0 ; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY; 15,000 UNITS DAILY; THIRD TRIMESTER INCREASE TO 20,000 UNITS DAILY) versus MIXED ABOVE/BELOW KNEE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at inpatients and up to 90 days from hospital discharge - Actual outcome for Pregnant women undergoing caesarean section and any other surgery during pregnancy or postpartum (including day case termination surgery and surgical management of miscarriage) : DVT at Up to hospital discharge; Group 1: 1/50, Group 2: 1/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at inpatients and up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death (including foetal death); occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (including adverse event for the foetus) at inpatient and up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with

	spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at inpatients and up to up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy (including the foetus) at inpatients and up to up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Segal 1975[293]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in Israel; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis:
Stratum	Pregnant or postpartum women not undergoing surgery: 90% vaginal delivery
Subgroup analysis within study	Not applicable:
Inclusion criteria	Women delivering vaginally or by caesarean section
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): Female. Ethnicity: Not reported
Further population details	1. Assisted conception: Not applicable 2. BMI : Not applicable 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=116) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously; 15,000 units daily; third trimester increase to 20,000 units daily). 5000U injected subcutaneously every 12 hours for 4-5 days after delivery. The initial heparin injection was given during active labour in 1/3 of the participants, the rest after delivery. In elective caesarean section, the heparin was given 2 hours before, at the end of surgery, and at 12 hour intervals, while in emergency caesarean the initial dose was administered immediately following the decision. Duration 4-5 days. Concurrent medication/care: Not reported (n=94) Intervention 2: No treatment - Usual care. Control group - no further details. Duration Not reported. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY; 15,000 UNITS DAILY; THIRD TRIMESTER INCREASE TO 20,000 UNITS DAILY) versus USUAL CARE

Protocol outcome 1: DVT (symptomatic) at 7-90 days from hospital discharge

- Actual outcome for Pregnant or postpartum women not undergoing surgery: DVT at 6 weeks; Group 1: 1/116, Group 2: 5/94 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at inpatients and up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at inpatients and up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death (including foetal death); occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (including adverse event for the foetus) at inpatient and up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at inpatients and up to up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy (including the foetus) at inpatients and up to up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

H.19 People with psychiatric illness

No relevant studies were identified.

H.20 Anaesthesia

H.20.1 Regional vs general anaesthesia

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Mitchell et al., 1991[226]	RCT	1+	Total: 72 Intervention : n = 34 Control: n = 38	Type of surgery: total knee arthroplasty Duration of surgery: Intervention : mean 122 min Control: mean 121 min Both study groups: Mean age: 64 (range38-84) yrs M/F:45/27 No between-group differences for age or sex	Type: Epidural anaesthesia Dose: Timing: Operative period Additional non-comparative prophylaxis: Males received 650mg aspirin beginning eve pre-surgery, females received adjusted dose warfarin PTT 15- 16 secs. All patients CPM machine daily and physical therapy	Type: General anaesthesia Dose: sodium theopental Timing: Operative period Additional non-comparative prophylaxis: Males received 650mg aspirin beginning eve pre-surgery, females received adjusted dose warfarin PTT 15- 16 secs. All	Scan performed up to day 8 after surgery	DVT Confirmed by: bilateral venography 6,7 and 8th post-op days	Int: 12/34 Control: 10/38 p value: Not significant All asymtomatic	Comments: Male patients received aspirin, female warfarin. No differences in sex between study groups, and incidence and distribution of DVT not affected by pharmacological prophylaxis. Not reported: PTS, bleeding, QoL, survival, funding
								Proximal DVT Confirmed by:	Incidence of Proximal DVT reported to be 46% in epidural and 63% in general anaesthesia groups. (actual numbers can"t be reliably calculated from these figures)	
								PE Confirmed by: V/Q scan on 6,7 and 8th post- op days	10% of patients reported as having positive V/Q scan, all asymptomatic. No information on group.	
								Length of Hospital Stay	Int: Mean 10.4 days	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
						patients CPM machine daily and physical therapy			Control: Mean 11.0 days p value: not reported	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Modig et al., 1981[228]	RCT	1+	Total: 30 Intervention: n = 15 Control: n = 15	Type of surgery: Total hip replacement (for severe osteoarthritis) Duration of surgery: Intervention: 147±27.9min Control: 161.3±34.5 min Intervention: Mean age: 66.5±5.5 yrs M/F:7/8 Control: Mean age: 65.4±6.3 M/F:8/7	Type: Continuous lumbar epidural block Dose: 0.5% bupivacaine with epinephrine (5µg/ml) Post op: 4-6 ml of 0.5% bupivacaine with epinephrine ever 4 hours for 16 hours Timing: Prolonged into post-op period for pain relief Additional non-	Type: General anaesthesia Dose: thiopentone Post-op: Parenteral analgesics on demand Timing: Intraoperatively. Additional non-comparative prophylaxis:	Scanning was performed 14 days before surgery and 14 days postoperatively	DVT Confirmed by: Bilateral venography on 14th post-op day	Int: 5/15 Control: 11/15 p value: 0.0281	Not reported: PTS, QoL, survival, LoS, funding
								Proximal DVT Confirmed by:	Int: 3/15 Control: 11/15 p value: <0.05	
								PE Confirmed by: all patients had V/Q scan on 14th post-op day	Int: 2/15 Control: 7/15 p value: Not significant Only 3 PEs (all in control group) were symptomatic	
								Bleeding related	Intraoperative blood loss:	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
					comparative prophylaxis: Physiotherapy program with early ambulation	Physiotherapy program with early ambulation		complications Intraoperative blood loss: (no measurement criteria) Post-operative blood loss: (no measurement criteria)	Int: 1100±316 ml Control: 1757±426ml p value: <0.001 (Significant) Postoperative blood loss: Int: 1200±350 ml Control: 1800±400 ml p value: <0.001 (Significant)	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Nielsen et al., 1990[239]	RCT	1+	Nos	Type of surgery:	Type: lumbar epidural	Type: general	Both	DVT Confirmed	Int: 2/13	Not reported: PTS,
			randomise	primary or revision	anaesthesia Dose:	anaesthesia	groups: 9-	by: bilateral	Control: 10/16	PE,QoL, survival,
			d:	knee arthroscopy	2% mepivacain	Dose:	11 days	ascending	p value: <0.05	LoS, funding

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			Total: 36	Duration of			post-op	venography on 9-		
			Intervention	surgery:	Additional non-	Additional non-		11th day post-op		
			: n = 18	Intervention: median	comparative	comparative		Proximal DVT Confirmed by: bilateral ascending venography on 9- 11th day post-op	Int: 1/13 Control: 3/16 p value: Not reported	
			Control: n	80 (55-100) min	prophylaxis: Thigh-	prophylaxis:				
			= 18	Control: min	length stocking on	Thigh-length				
					contralateral leg pre-	stocking on				
			7 patients	Intervention:	op until full	contralateral leg				
			withdrawn	Median age: 70	ambulation. Calf-	pre-op until full				
			– 5	(range 46-87) yrs	length stocking on	ambulation. Calf-				
			epidural, 2	M/F:5/13	operated leg	length stocking on		Bleeding related complications Suction drain volume	Median suction drain volume: Int: 1060 (340-1940) ml Control: 990 (195-3275) p value: >0.4 Not significant	
			general		immediately post-op	operated leg				
				Control: Median	until ambulation. Quad	immediately post-				
				age: 65 (range38-	exercises on 1st post-	op until				

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				85) M/F:6/12	op day, active knee	ambulation. Quad				
					mobilisation with full	exercises on 1st				
				Pre-existing risk	weight bearing from	post-op day,				
				factors: Cardiac	2nd day.	active knee				
				disease, varicose		mobilisation with				
				veins. Higher BMI in		full weight				
				control group		bearing from 2nd				
						day.				

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Poikolainen and Hendolin 1983[264]	RCT	1+	Total: 38 Intervention : n = 17 Control: n = 21	Type of surgery: Prostatectomy Duration of surgery: Intervention: 71±3 min Control: 74±3 min	Type: lumbar epidural anaesthesia Dose: Butanilicaine 2% Additional non-comparative prophylaxis: Not	Type: General anaesthesia Dose: Thiopentone	NR	DVT Confirmed by: 125I FUT test (timing NR). Positive result confirmed by venography	Int: 2/17 Control: 11/21 p value: <0.02 (Significant)	Comments: Study measured changes in flow velocity in femoral vein. Induction of epidural anaesthesia led

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				Intervention: All male Mean age: NR. No differences between groups for age Control: All male Mean age: NR. No differences between groups for age Pre-existing risk factors: NR. No differences between groups	reported					to significant increase in velocity of blood flow in femoral vein ($p<0.001$), whereas flow velocity fell significantly with general anaesthesia.

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[276]	Systematic Review	1+	Total: 939	Type of surgery:	Regional Anaesthesia	General	Between 4	DVT confirmed by	Int : 130/417	Not reported: LoS,
			Int:367	General (1 study)		Anaesthesia	to 14 days	venograph or	Cont: 198/416	QoL and PTS.

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
11 RCT Studies [35,77,78,107,144,145,158,221,227,277,338] All of these studies were included in the guideline review.	w		Cont: 384	Urological (1 study)			postoperati	fibrinogen uptake	p value: 0.0000	
				Orthopaedic (9	Timing: Ranged from	Timing: Ranged	vely	PE confirmed by scan	Int : 21/281 Cont: 32/264 (reported in 6 studies) p value: 0.0672	
			Misc: 188	studies)	73 mins to 3 days	from 79 – 150				
			(not			mins.				
			reported		Not addressed in 4					
			number in		studies	Not addressed in				
			each arm)			6 studies.				
								Major bleeds	Int : 0/317 Cont: 5/315 (reported in 7 studies) p value: 0.0243	
					Additional non-					
					comparative prophylaxis:	Additional non-comparative prophylaxis:				
					LMWH + GCS (one study);	LMWH + GCS (one study);				
					GCS (two studies);			Proximal DVTs	Int : 14/268 Cont: 47/253 (reported in 6 studies) p value: 0.0000	
					Dextran 70 (one study);	GCS (two studies); Dextran 70				

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
						(one				
					Dextran 40 + 7500 IU	study);				
					H (one study);	Dextran 40 +				
					ASA, GCS on no-op	7500 IU H (one				
					limb (one study).	study);				
						ASA, GCS on no-				
						op limb (one				
						study).				

H.20.2 Regional + general vs general anaesthesia

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Dauphin et al.,	RCT	1+	Total: 37	Type of surgery:	Type: General	Type: General	Daily 125I	DVT Confirmed	Int: 4/20	Comments:
1997[76]				Total hip	anaesthesia plus	anaesthesia	scan for 3	by: 125I FUT test	Control: 4/17	Possible error in
			Intervention	arthroplasty	lumbar epidural	Dose: Thiopental	days,	daily for 3 days	p value: 0.79	standard deviation
			: n = 20		anaesthesia Dose:	sodium. Specific	impedence	post-op.		of surgery duration

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				Duration of	General: Thiopental	drug and dose	plethysmog	Venography on		in control group
			Control: n	surgery: Intervention	sodium. Specific drug	chosen by	raphy on	day of discharge		(5.3hrs!). Paper
			= 17	2.28±0.27 hr.	and dose chosen by	anaesthesiologist	days 5,7			reports no
			(40	Control: 2.5±5.3	anaesthesiologist		and 9 and			significant
			randomised		Epidural: 10 ml 0.5%	Timing: For the	venograph			difference between
			– 3 drop-	Intervention: Mean	bupivacaine	operative period	y on the			the two groups in
			outs)	age: 70.9±6.7 yrs			planned			operation length.
				M/F:7/13	Timing: For the	Additional non-	day of	Bleeding related	Intraoperative	Not reported:
					operative period	comparative	discharge	complications	blood loss:	
				Control: Mean age:		prophylaxis:		Intraoperative	Int: 663.8±299.0	Proximal DVT, PE,
				66.2±14.3	Additional non-	Coumadin daily		blood loss: sponge	Control:	PTS, QoL, LoS,
				M/F:7/10	comparative	from 1st post-op		weights and	1259.2±366.0	survival
					prophylaxis:	day until		suction bottle	p value: <0.001	
					Coumadin daily from	discharge.		contents		

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
					1st post-op day until discharge.			Post-operative blood loss: measured from wound drainage (using the Dalvol Reliavac 400 system)	Post-operative blood loss: Int: 444.0±300.8 Control: 600.8±390.8 p value: 0.18 Total blood loss: Int: 1107.8±378.6 Control: 1860.0±616.6 p value: <0.001	

H.21 Lower limb immobilisation

Study	Domeij-arverud 2013[87]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=26)

Study	Domeij-arverud 2013[87]
Countries and setting	Conducted in Sweden; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 2+6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Acute unilateral tendo Achillis rupture operated on within 72 hours; aged 18-75 years
Exclusion criteria	Inability to give informed consent; ongoing anticoagulation treatment; planned follow-up at another hospital; inability to follow instructions; known kidney failure; heart failure with pitting oedema; thrombophlebitis; any thromboembolic event during the previous 3 months; other surgery in past month; known malignancy; haemophilia; pregnancy; unwillingness to participate
Recruitment/selection of patients	Between February and December 2010
Age, gender and ethnicity	Age - Mean (range): intervention 39.8, control 40.4 (range 27-50). Gender (M:F): 1:1. Ethnicity: not reported
Further population details	1. Active cancer: No active cancer (people with known malignancy excluded). 2. BMI: Mixed (intervention mean 27.2 (range 21.9-39.1), control mean 24.3 (range 19.9-29.4)). 3. Renal impairment: No renal impairment (eGFR greater than 30ml/min/1.73m2) (people with known kidney failure excluded). 4. Weight bearing: Not stated
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Intermittent pneumatic compression devices - Below knee. Foot IPCD beneath plaster cast. Duration 2 weeks post-op (mean 79.5 hours; SD 38; range 29 to 152 hours). Concurrent medication/care: Plaster cast, below knee (n=12) Intervention 2: No treatment - Usual care. No prophylaxis. Duration 2 weeks post-op. Concurrent medication/care: Plaster cast, below knee
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT. Confirmed with colour Doppler sonography at 42 days; Group 1: 8/10, Group 2: 5/12; Risk of bias: Very high; Indirectness of outcome: No

Study	Domeij-arverud 2013[87]
indirectness Protocol outcome 2: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at 42 days; Group 1: 0/12, Group 2: 0/12	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study

Study	Domeij-arverud 2015[86]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Sweden
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-75 years; sustained an acute unilateral rupture of the Achilles tendon and had undergone surgery within 96 hours of injury
Exclusion criteria	inability to give informed consent; anticoagulation treatment (including high dose aspirin); planned follow up at another hospital; renal failure; heart failure with pitting oedema; thrombophlebitis; thromboembolic event during the

Study	Domeij-arverud 2015[86]
	last 3 months; other surgery during the previous month; malignancy; haemophilia; pregnancy
Recruitment/selection of patients	Between March 2011 and June 2013
Age, gender and ethnicity	Age - Mean (range): 40.9 (26-62). Gender (M:F): 88:21. Ethnicity: not reported
Further population details	1. Active cancer: No active cancer (people with malignancy excluded). 2. BMI : Mixed (mean 27.1 (range 21-41.2)). 3. Renal impairment: No renal impairment (eGFR greater than 30ml/min/1.73m2) (people with renal failure excluded). 4. Weight bearing: Not applicable (allowed to weight bear as tolerated).
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Intermittent pneumatic compression devices - Below knee. Bilateral IPCD of calf for 6 hours daily, on operated leg this was applied under the plaster cast. Duration 2 weeks. Concurrent medication/care: Plaster cast (n=74) Intervention 2: No treatment - Usual care. No prophylaxis. Duration 2 weeks. Concurrent medication/care: Plaster cast
Funding	Other (Stockholm County Council and Karolinaska Institutet; Swedish National Centre for Sports Research; Swedish Research Council; DJO Vista, California)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT in operated leg confirmed by compression duplex ultrasound at 6 weeks; Group 1: 36/69, Group 2: 34/71; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE, clinical at 6 weeks; Group 1: 0/69, Group 2: 0/71; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at 6 weeks; Group 1: 0/69, Group 2: 0/71	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or

Study	Domeij-arverud 2015[86]
	life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Jorgensen 2002 [160] Country of study: Denmark Study design: RCT List who was masked to interventions: assessors of venograms Evidence level: 1+ Duration of follow-up:	Patient group: Patients wearing below knee plaster casts on lower extremity (reasons for plaster cast: fracture (n=220); tendon ruptures (n=61); other (n=19) Setting: Outpatients Inclusion criteria: age >18 planned lower limb plaster cast of at least 3 weeks Exclusion criteria: pregnancy allergy to heparin or contrast media known liver or renal impairment uncontrolled hypertension bleeding disorders cerebral insults due to bleeding recent gastrointestinal bleeding	Group I LMWH tinzaparin (Innohep) 3500 IU self-injected into abdominal wall once daily until plaster cast removed. Mean duration 5.5 weeks. Group II no LMWH Additional non-comparative prophylaxis: None	DVT, asymptomatic or symptomatic (diagnosed by ascending unilateral venography when plaster cast removed)	Group 1: 10/99 Group 2: 18/106 P value: 0.15	Funding: not reported Limitations Only assess one leg for DVT; patients and clinicians not masked to treatment; the reasons for two thirds of patients not reaching an endpoint are not clear for all patients Outcomes not reported: major and minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life Additional outcomes
			DVT, asymptomatic or symptomatic by diagnosis (diagnosed by ascending unilateral venography when plaster cast removed)	Fractured patients Group 1: 8/73 Group 2: 10/77 P value: 0.70 Tendon ruptured patients Group 1: 2/20 Group 2: 6/21 P value: 0.24 Patients operated on Group 1: 9/86 Group 2: 16/89 P value: 0.16	
			Above knee DVT (diagnosed by ascending unilateral venography when plaster cast removed)	Group 1: 0/99 Group 2: 1/106 P value: not significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
while wearing plaster cast (mean duration 5.5 weeks)	inability to self-inject All patients N: 300 No. of dropouts: 95 Group I No. randomised: 148 No. of dropouts: 49 Age (mean): 49 M/F: 69/79 BMI: 25 Additional risk factors: smokers 67; oral contraceptives 7; previous DVT 3; varicose veins 5; cardiac diseases 1 Other factors: no. having an operation 86 (58%) Group II No. randomised: 152 No. of dropouts: 46 Age (mean): 46 M/F: 59/93 BMI: 25 Additional risk factors: smokers 73; oral contraceptives 6; previous DVT 3; varicose veins 15; cardiac diseases 3 Other factors: no. having an operation 89 (59%)		Symptomatic DVT (confirmed by ascending unilateral venography when plaster cast removed)	Group 1: 0/99 Group 2: 1/106 P value: not significant	reported: Bleeding-4 hematomas (uncertain which arm) and 1 metroharrgia in LMWH arm. No. of DVTs by type of injury , no. of DVTs in those having surgery; about 60% reported no difficulty with self-injection; mean pre- and post-study platelet count; mean aspartate and alanine amino transferase, mean alkaline phosphatise Main reasons for not reaching an endpoint: discomfort with self-injection 18/95, metrorrhagia 1/95, refuse phlebography 12/95, venograph not possible or refused 26/95, miscellaneous 38/95 Notes: Bleeding data – excluded due to ambiguity in reporting
			Symptomatic pulmonary embolism	Group 1: 0/99 Group 2: 0/106 P value: not significant	
			Wound infection	Group 1: 4/99 Group 2: 1/106 P value: not significant	
			Discomfort with self-injection – stopped study	Group 1: 18/148 Group 2: Not applicable 18/95 of total drop outs due to discomfort in self injection	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					and definition after discussions between reviewers.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kock 1995 [175] Country of study: Germany Study design: RCT List who was masked to interventions: nobody Evidence level: 1+ Duration of follow-up: until plaster cast removed	Patient group: Patients with leg injury for which conservative treatment without admission to hospital was indicated. Below knee cast (n=366) or above knee casts (n=62). Reasons for plaster cast: Grade II sprains and bruises (n=122); Grade III sprains (n=130); fractures (n=72); other (n=15) Setting: Outpatients Inclusion criteria: ■ age 18-65 Exclusion criteria: previous DVT pregnancy clotting disorders or anticoagulant medication bleeding sources contraindications to heparin chronic venous insufficiency plaster cast after surgery	Group I LMWH (Mono-Embolex NM (Sandoz) 0.3ml per syringe with an activated partial thrombo-plastin time activity of 1500 units & anit-Xa activity of 3000 units. Not reported when started, self-injected until plaster cast removed Group II no LMWH Additional non-comparative prophylaxis:	DVT, asymptomatic or symptomatic (* confirmed by venography when plaster cast removed)	Group 1: 0/176 Group 2: 7/163 P value: 0.06	Funding: not reported Limitations Nobody masked to treatment. Does not report initial numbers randomised to each group Outcomes not reported: mortality, pulmonary embolism, minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life Additional outcomes reported: DVT sub grouped by
			Proximal DVT (as above)	Group 1: 0/176 Group 2: 3/163 P value: NS	
			Calf DVT (as above)	Group 1: 0/176 Group 2: 4/163 P value: NS	
			Mean (+SD) duration of plaster-cast immobilisation (days)	Group 1: 15.2 +12 (n=176) Group 2: 18.8 +13 (n=163) P value: 0.008	
			Mean (+SD) duration of plaster-cast immobilisation (days)	Patients with DVT: 11.4 +10 (n=7) Patients without DVT: 17.2 +13 (n=332) P value: 0.13	
			Major bleeding (not defined)	Group 1: 0/176 Group 2: 0/163 P value: n/a	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients N: 428 No. of dropouts: 89 Group I No. randomised: NR No. of dropouts: NR Age (mean): 34.1 (18-63) M/F: 104/72 Weight (mean): 78.4 +13 kg Additional risk factors: age >40 (n=53); obesity (Broca index >1.2) (n=40); cigarette smoking (n=83); varicose veins (n=23); oral contraceptives (n=18); Group II No. randomised: NR No. of dropouts: NR Age (mean): 33 (18-63) M/F: 104/59 Weight (mean): 75.0 +14 kg Additional risk factors: age >40 (n=44); obesity (Broca index >1.2) (n=34); cigarette smoking (n=70); varicose veins (n=31); oral contraceptives (n=25)	None			risk factor Notes: * DVT checked by clinical examination, measurement of leg circumference, venous occlusion plethysmography, B-mode compression ultrasonography and duplex scanning and confirmed by venography

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kujath 1993 [179]	Patient group: Outpatients with leg injury treated conservatively and immobilisation by	Group I LMWH (Fraxiparin) 0.3ml	DVT, asymptomatic or symptomatic (diagnosed by ultrasound confirmed	Group 1: 6/126 Group 2: 21/127 P value: <0.01	Funding: not reported

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: Germany Study design: RCT List who was masked to interventions: no one Evidence level: 1+ Duration of follow-up: until plaster cast removed	plaster cast. Type of injury: soft tissue (n=176); fractures (n=77) Setting: Outpatients Inclusion criteria: age >16 immobilisation by plaster cast for at least 7 days Exclusion criteria: known thrombopathy oral anticoagulation fresh brain or gastrointestinal bleeding acute pancreatitis inflammatory heart disease All patients N: 306 No. of dropouts: 53 Group I No. randomised: 126 No. of dropouts: NR Age (mean): 32.9 +13.8 M/F: 69/57 Weight (mean): 73.7 +14.2 kg Additional risk factors: history of thrombosis or embolism (n=9); age >40 (n=31); overweight (n=34);	daily [36mg heparin fraction calcium, molecular mass 4000-5000. Started on first day of treatment, continued until plaster cast removed Group II no LMWH Additional non-comparative prophylaxis: None	by venography) Mean (+SD) duration of plaster-cast (days)	 Group 1: 15.6 +6.8 (n=126) Group 2: 15.8 +9.6 (n=127) P value: 0.85	Limitations Nobody masked to treatment. Outcomes not reported: mortality, pulmonary embolism, minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life Additional outcomes reported: DVT subgrouped by risk factor; total no. of symptomatic DVTs 9/27 (not given by group) Notes:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	smoking (n=48); varicose veins (n=18); oral contraceptives (n=8); Group II No. randomised: 127 No. of dropouts: NR Age (mean): 35.6 +14.6 M/F: 77/50 Weight (mean): 74.4 +13.6 kg Additional risk factors: history of thrombosis or embolism (n=6); age >40 (n=44); overweight (n=36); smoking (n=45); varicose veins (n=15); oral contraceptives (n=13);				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lapidus 2007A[185] Country of study: Sweden Study design: Single centre, double blinded RCT List who was masked to interventions: Investigators,	Patient group: Achilles tendon rupture, all received surgery. Setting: Stockholm Soder Hospital (Nov2001-May2004) Inclusion criteria: Consecutive patients 18-75 years old Admitted because of Achilles tendon rupture (0- 72h) and accepted for surgery Exclusion criteria: Inability or refusal to sign informed consent	Group 1 LMWH Dalteparin 5000U Group 2 Placebo (9%w/v sodium chloride), 0.2 ml in identical syringes to dalteparin. Frequency: once daily Route: subcutaneous injection Start time: Within	All-cause mortality (confirmed by: No death was reported)	Group1: 0/52 Group 2: 0/53 P value: 1.0	Funding: Pfizer/Pharmacia and Karolinska Institute provided grants. Dalteparin provided by Pharmacia/ Pfizer Limitations: Positive events detected by CDS, but not confirmed by phlebography (either not performed or not interpretable) had not been included in the primary and secondary analysis of efficacy Only the affected leg was
			Fatal pulmonary embolism (confirmed by: None reported)	Group1: 0/52 Group 2: 0/53 P value: 1.0	
			Symptomatic pulmonary embolism (confirmed by: ventilation perfusion scan or spiral CT if suspected)	Group1: 0/52 Group 2: 0/53 P value: 1.0	
			DVT, asymptomatic or symptomatic (screened for by: unilateral ascending	(As reported) Up to Week 6 (by	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
patients, radiologist who carried out standardised final evaluation Evidence level: 1+ Duration of follow-up: Up to 6 weeks	form Ongoing treatment with anticoagulant Known allergy to contrast media Planned follow up at another hospital Recent surgery or thromboembolic event (during the proceeding 3 months) Known malignancy Current bleeding disorder Pregnancy Treatment with high doses of acetyl salicylic acid (≥325 mg) or other platelet inhibitors Other injuries All patients N: 105 Age (mean): 40 years M/F: 83/22 Time to surgery (mean): 2days VTE history : 0/105 Surgery method: Usually short skin incision placed medially over the rupture, end to end suture most commonly with modified Kessler technique. Plaster cast: Below knee plaster cast with ankle in the equinus position. At 3rd week, this was replaced by another plaster cast or orthoses at neutral position. Anaesthesia: spinal or local	hours post-surgery End time: up to 6th week, or mobilisation Duration: up to 6 weeks after surgery All patients given 45 syringes. Additional non-comparative prophylaxis: Not mentioned	phlebography of the affected legs, or colour duplex sonography (CDS) when phlebography fails at the 3rd week and 6th week, on the last day of the dose (or a day after), and when thrombosis is suspected, whichever earlier.	phlebography) ITT analysis Group1: 16/47 (34%) Group 2: 16/44 (36%) P value:0.8 Up to Week 6 (by phlebography or CDS), ITT analysis1 Group1: 18/49 (37%) Group 2: 19/47(40%) P value: 0.8 Note: 24 (65% diagnosed at week 3, the rest at the end of study) [value calculated by NCC- AC team using Fishers' exact test]	scanned routine scanning Outcomes not reported: Symptomatic DVT, Thigh DVT; Fatal or neurological or upper GI bleeding, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay Additional outcomes reported: Details/reasons for patients to be non-evaluable. Compliance with extended LMWH injections, duration of immobilisation, mean time to DVT diagnosis Number of patients treated for DVT was reported as 20/49 (40%) in the treatment and 23/47(43%) in the placebo arms respectively. An additional 1 patient from each arm was treated but not included in the ITT analysis. Notes: All admitted Achilles tendon
	Group 1		Thigh DVT (screened for by: as above, defined as affecting popliteal vein or any other more proximal vein, with or without involvement of the calf veins)	Group1: 1/49 Group 2: 3/47 P value: 0.6	
			Fatal bleeding (description: no death or major bleeding reported)	Group1: 0/52 Group 2: 0/53 P value: 1.0	
			Major bleeding (description: requiring	Group1: 0/52 Group 2: 0/53	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 52 No. of dropouts: 2 M/F: 41/11 Age (years): 37±8 Weight (kg): 80±12 BMI (kg/m2): 26±3 Time in surgery (min): 44±18 Torniquet used, time (min): 6/52, 34±14 Local/spinal anaesthesia:48/4 Smokers:9/52, 8/53 Hormonal contraceptives: 0/11, 1/11 Diabetes: 0/52, 2/53 Varicose veins: 3/52, 6/53 Orthosis used:12/52 Group 2 No. randomised: 53 No. of dropouts : 2 M/F: 42/11 Age (years): 42±9 Weight (kg): 81±11 BMI (kg/m2): 26±3 Time in surgery (min): 45±18 Torniquet used, time (min): 6/53, 39±17 Local/spinal anaesthesia:48/5 Smokers:8/53 Hormonal contraceptives: 1/11 Diabetes: 2/53 Varicose veins: 6/53 Orthosis used : 15/53		blood transfusion/ surgery, or at a critical site such as intracranial, intraocular, intraspinal, or retroperitoneal) Minor bleeding (description: A nose bleed)	P value: 1.0 Group1: 1/ 52 Group 2: 0/53 P value: 1.0	rupture patients l who required surgery was assessed for eligibility (n=285), and 257 fulfilled criteria. Patients with asymptomatic DVT detected by CDS but not verified by phlebography were excluded (n=5, 4 in placebo) Subjects were trained in self-injection by study nurse in hospital. Patients were followed up at 3 weeks after surgery, where plaster casts were changed and screening for DVT was done, and screened again at the end of study

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lapidus 2007B[186]	Patient group: Acute ankle fracture, all received	Group 1 LMWH	All-cause mortality (confirmed by: No death was	Group1: 0/136 Group 2: 0/136	Funding: Pfizer/Pharmacia and

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: Sweden Study design: Double blinded RCT List who was masked to interventions: All Evidence level: 1+ Duration of follow-up: Up to 6 weeks	surgery A majority of patient used plaster casts, 18% used orthosis Setting: Stockholm Soder Hospital (May2000-March2004) Inclusion criteria: 18-75 years old Admitted because of acute ankle (0-72h) fracture accepted for surgery Exclusion criteria: Inability or refusal to sign informed consent form Ongoing treatment with anticoagulant therapy Known allergy to contrast media Planned follow up at another hospital Recent surgery Known malignancy Current bleeding disorder Pregnancy Treatment with high doses of acetyl salicylic acid (≥325 mg) or other platelet inhibitors Multi-trauma (injuries involving >1 organ system in addition to the musculoskeletal system or multiple fractures)	Dalteparin 5000U, once daily Subcutaneous injection Group 2 Placebo(9%w/v sodium chloride), 0.2 ml in identical syringes to dalteparin. Start time: 7 days post-surgery End time: until plaster cast removed (mean 44 days±2) Duration: up to 6 week after surgery Additional non-comparative prophylaxis: Both groups received 5000Uof s/c dalteparin once daily for 7 days, starting on evening after surgery.	reported)	P value: 1.0	Karolinska Institute provided grants Limitations: Randomisation method and concealment not described. Only the affected leg was scanned. Baseline risk factors and comorbidities not reported Outcomes not reported: Calf DVT, minor bleeding, heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay Additional outcomes reported: Details/reasons for patients to be non-evaluable Compliance, duration of immobilisation, subgroup analysis of orthosis and casts Average age of patients
			Fatal pulmonary embolism (confirmed by: None reported)	Group1: 0/136 Group 2: 0/136 P value: 1.0	
			Symptomatic pulmonary embolism (confirmed by: ventilation perfusion scan or spiral CT if suspected)	Group1: 0/136 Group 2: 0/136 P value: 1.0	
			Symptomatic DVT (confirmed by: phlebography or CDS whenever indicated) One of the 8 events is a calf muscle vein thrombosis, not specified which arm	Group1: 2/136 Group 2: 6/136 P value: 0.28 Plaster cast subgroup: Group 1: 2/114 Group 2: 6/108 P value: 0. 16 [value calculated by NCC-AC team using Fishers' exact test]	
			DVT, asymptomatic or symptomatic (screened for by: unilateral ascending phlebography of the affected legs, or colour duplex sonography (CDS) when phlebography fails at 2nd and 6th week, on the last day of the dose (or a day after), and when thrombosis is suspected, whichever earlier.	Up to Week 6 (by phlebography) ITT analysis Group1: 21/101 (21%) Group 2: 27/96 (28%) P value:0.2 Up to Week 6 (by phlebography), per protocol Group1: 13/75 Group 2: 17/65 P value:0.2	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients N: 272 Age (mean): 48 (18-76) years M/F: 124/148 Group 1 No. randomised: 136 No. of dropouts (non-evaluable): 35 M/F: 62/74 Patients Age (years): 49±14 Weight (kg): 80±16 BMI (kg/m2): 27±4 Time in surgery (min): 65±28 Tourniquet time (min): 70±28 Fracture type: - Unimalleolar: 59/136 (43%) - Bimalleolar: 42/136 (31%) - Trimalleolar: 35/136 (26%) Used plaster cast: 114/136 Group 2 No. randomised: 136 No. of dropouts (non-evaluable): 40 M/F: 62/74	All received 1000mL Dextran 60 on admission		Up to Week 6 (by phlebography or CDS, ITT analysis) Group1: 24/117 Group 2:34/109 P value:0.07 Plaster cast subgroup Up to Week 6 (by phlebography) ITT analysis Group1: 18/86 Group 2: 27/75 P value: 0.04 Up to Week 6 (by phlebography), per protocol Group1: 21/99 Group 2: 33/86 P value: 0.02	who used an orthosis was 45 years p=0.03 compared to plaster cast patients Notes: All subjects were trained in self-injection by as study nurse before leaving hospital. All ankle fracture patients admitted to hospital who
			Thigh DVT (screened for by: as above, defined as affecting popliteal vein or any other more proximal vein, with or without involvement of the calf veins)	Group1: 4/101 Group 2: 3/96 P value: 0.2	
			Fatal bleeding (description: no death or major bleeding reported)	Group1: 0/136 Group 2: 0/136 P value: 1.0	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (years): 48±14 Weight (kg): 78±13 BMI (kg/m2): 26±3 Time in surgery (min): 63±28 Torniquet time (min): 68±30 Fracture type: - Unimalleolar: 44/136 (32) - Bimalleolar: 53/136 (39) - Trimalleolar: 39/136 (29) Used plaster cast: 108/136		Major bleeding (description: requiring blood transfusion/ surgery, or at a critical site such as intracranial, intraocular, intraspinal, or retroperitoneal)	Group1: 0/136 Group 2: 0/ 136 P value: 1.0 Plaster cast subgroup: Group 1: 0/114 Group 2: 0/108	
			Minor bleeding (description: All local bleedings not classified as "major bleeding")	Group1: 1/ 136 Group 2: 1/136 P value: 1.0	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lassen 2002 [192] Country of study: Denmark Study design: RCT List who was	Patient group: Outpatients with fracture of the leg or rupture of the Achilles tendon requiring at least five weeks immobilisation in plaster cast or brace within 4 days of injury. Setting: Outpatients Inclusion criteria: age >18	Group I LMWH (Reviparin, 1750 anti-Xa units self-injected daily Started not more than more 4 days after fractures and continued throughout immobilisation. Group II	DVT, asymptomatic or symptomatic (diagnosed by unilateral venography within a week of plaster cast removal)	Group 1: 17/183 Group 2: 35/188 P value: 0.01	Funding: supported by grant from Knoll Limitations Appears a fairly well conducted study Outcomes not reported: mortality,
			Symptomatic DVT (confirmed by unilateral venography)	Group 1: 0/217 Group 2: 4/221 P value:	
			Proximal DVT (diagnosed by unilateral venography within a	Group 1: 3/183 Group 2: 10/188	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
masked to interventions: Patients and investigators of venography Evidence level: 1+ Duration of follow-up: until plaster cast removed	requiring lower limb cast >5 weeks Exclusion criteria: weight <35kg pre-existing venous thromboembolism systolic blood pressure >200mmHg diastolic blood pressure >110mmHg cerebral vascular aneurysm cerebral vascular accident within preceding 3 weeks active gastroduodenal ulcer haemorrhagic diathesis bacterial endocarditis platelet count <100,000 per mm3 previous treatment with heparin lasting >4 days ■ previous treatment with fibrinolytic agents or oral anticoagulants ■ immobilisation for >4 days before enrolment ■ known hypersensitivity to heparin or contrast medium contraindications to venography myocardial infarction in previous 3 months multiple myeloma current pregnancy or lactation current treatment with any investigational drug or such treatment within preceding 4 weeks	Placebo Additional non-comparative prophylaxis: Patients who underwent surgery were permitted to have had heparin treatment lasting up to 4 days before randomisation. Numbers treated Group I: 65 Group II: 71	week of plaster cast removal)	P value: 0.09	pulmonary embolism, minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life Notes: Discussed between reviewers: Major bleeding included "minor bleeding" cases where treatment was discontinued, based on author's definition. Denominator for Group 1 set as 217 – the number randomised to be consistent as ITT. Paper reported safety population based on 438, but unclear which were the patients excluded.
			Distal DVT (diagnosed by unilateral venography within a week of plaster cast removal)	Group 1: 14/183 Group 2: 25/188 P value: 0.09	
			Symptomatic pulmonary embolism (confirmed by ventilation perfusion scanning)	Group 1: 0/217 Group 2: 2/221 P value: NS	
			Major bleeding (defined as clinically apparent bleeding associated with a decrease of at least 2.0g per deciliter in the haemoglobin level, requirement for transfusion of at least 2 units of packed red cells, or retroperitoneal or intracranial bleeding or other bleeding that investigators decided required permanent discontinuation of treatment)	Group 1: 2/217 Group 2: 1/221 P value: NS	
			Minor bleeding (defined as bleeding not meeting definition for major bleeding)	Group 1: 12/217 Group 2: 11/221 P value: NS	
			Mean (+SD) duration of	Group 1: 43 (n=126)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	[redacted] history of drug or alcohol abuse All patients N: 440 No. of dropouts: 69 Group I No. randomised: 217 No. of dropouts: 34 (reasons: withdrew consent 2; adverse events 1; venograms not evaluable 31) Age (median, interquartile range): 47 (37-55) M/F: 112/105 BMI (median, interquartile range): 25 (23-28) kg/m2 Additional risk factors: previous thromboembolism (n=5); varicose veins (n=20); hypertension (n=13); hypercholesterolemia (n=14); oral contraceptives (n=14); current hormone replacement therapy (n=8); diabetes mellitus (n=5); smoking (n=79) Type of injury: tibial fracture (n=18), patellar fracture (n=7); malleolar fracture (n=127); fracture in the foot (n=15); rupture of Achilles tendon (n=52) Surgical treatment: 118		immobilisation (days)	Group 2: 44 (n=127) P value: NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group II No. randomised: 223 No. of dropouts: 35 (reasons: no injections 2; adverse events 3; venograms not evaluable 30) Age (median, interquartile range): 47 (37-56) M/F: 114/109 BMI (median, interquartile range): 26 (24-28) kg/m2 Additional risk factors: previous thromboembolism (n=5); varicose veins (n=21); hypertension (n=22); hypercholesterolemia (n=15); oral contraceptives (n=11); current hormone replacement therapy (n=9); diabetes mellitus (n=5); smoking (n=105) Type of injury: tibial fracture (n=10), patellar fracture (n=8); malleolar fracture (n=155); fracture in the foot (n=13); rupture of Achilles tendon (n=36) Surgical treatment: 126				

Study	POT-CAST trial: Van adrichem 2016[322]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1519)
Countries and setting	Conducted in Netherlands; Setting: 10 hospitals in the Netherlands (7 teaching hospitals, 2 private medical care clinics, and 1 academic medical centre)

Line of therapy	1st line
Duration of study	Intervention + follow up: Immobilisation + 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Surgical or non-surgical treatment
Inclusion criteria	Patients 18 years or older who presented to the emergency department and were treated for at least 1 week with casting of the lower leg (with or without surgery before or after casting but without multiple traumatic injuries).
Exclusion criteria	Previous VTE, contraindications to LMWH, pregnancy, and current use of anticoagulant therapy for other indications (although the use of antiplatelet drugs were allowed).
Recruitment/selection of patients	March 2012 through January 2016 patients treated with casting of the lower leg who were enrolled in 8 trial centres.
Age, gender and ethnicity	Age - Mean (SD): LMWH 46.5 (16.5); No proph 45.6 (16.4). Gender (M:F): 716/719. Ethnicity: NR
Further population details	1. Active cancer: Mixed (Treatment group 34/674 cancer; Control group 29/674 cancer.). 2. BMI : Mixed (Treatment group 26.0 (4.4); Control group 25.7 (4.4).). 3. Renal impairment: Not applicable 4. Weight bearing: Not applicable
Extra comments	Duration of casting (wk): treatment group 4.9 (2.5); control group 4.9 (2.5) Indication for casting: Fracture 89%, Achilles' tendon rupture 7%, ankle distortion 2%, antalgic gait 1%, contusion 1% Surgery:treatment group 13%; control group 11%
Indirectness of population	No indirectness
Interventions	(n=761) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin or Nadroparin (according to the preference of the hospital). First dose of LMWH administered in the emergency department. 2850 IU of nadroparin or 2500 IU of dalteparin was used for people who weighed 100kg or less, and a double dose (in one daily injection) was used for patients who weighted more than 100kg. Duration the full period of immobilisation. Concurrent medication/care: NR

	(n=758) Intervention 2: No treatment - Placebo. No anticoagulation therapy. Duration duration of study. Concurrent medication/care: NR
Funding	Academic or government funding (Supported by the Netherlands Organization for Health Research and Development.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus PLACEBO

Protocol outcome 1: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Symptomatic PE: no definition reported at 3 months; Group 1: 3/719, Group 2: 4/716
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 42, Reason: 14 excluded due to inclusion/exclusion criteria. Plus lost to follow-up and withdrew consent (unclear proportion of which); Group 2 Number missing: 42, Reason: 19 excluded due to inclusion/exclusion criteria. Plus lost to follow-up and withdrew consent (unclear proportion of which)

Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding: no definition reported at 3 months; Group 1: 0/719, Group 2: 0/716
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 42, Reason: 14 excluded due to inclusion/exclusion criteria. Plus lost to follow-up and withdrew consent (unclear proportion of which); Group 2 Number missing: 42, Reason: 19 excluded due to inclusion/exclusion criteria. Plus lost to follow-up and withdrew consent (unclear proportion of which)

Protocol outcome 3: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge
- Actual outcome: Clinically relevant non-major bleeding: no definition reported at 3 months; Group 1: 1/719, Group 2: 0/716
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 42, Reason: 14 excluded due to inclusion/exclusion criteria. Plus lost to follow-up and withdrew consent (unclear proportion of which); Group 2 Number missing: 42, Reason: 19 excluded due to inclusion/exclusion criteria. Plus lost to follow-up and withdrew consent (unclear proportion of which)

Protocol outcome 4: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: Symptomatic DVT at 3 months; Group 1: 6/719, Group 2: 8/716 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 42, Reason: 14 excluded due to inclusion/exclusion criteria. Plus lost to follow-up and withdrew consent (unclear proportion of which); Group 2 Number missing: 42, Reason: 19 excluded due to inclusion/exclusion criteria. Plus lost to follow-up and withdrew consent (unclear proportion of which)	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Unplanned return to theatre at up to 45 days from hospital discharge

Study	**PROTECT trial: Bruntink 2017[36]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=467)
Countries and setting	Conducted in Netherlands; Setting: Seven Dutch hospitals
Line of therapy	1st line
Duration of study	Intervention time: Duration of immobilisation ~39 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Thromboprophylaxis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (≥18 years) diagnosed with a fracture of the ankle or foot who required non-surgical treatment with immobilisation in a below-knee plaster cast for a minimum of four weeks.

Exclusion criteria	A delay between injury and the emergency department visit of more than 72 hours; a known hypersensitivity to nadroparin or fondaparinux; a history of VTE; already on continuous anticoagulation therapy; hypercoagulability; a bleeding tendency/disorder; pregnancy or lactation; active malignancy; severe hepatic or renal impairment; retinopathy; previous or active bleeding from the digestive tract; haemorrhagic stroke within the previous 2 months; intraocular/spinal/brain surgery within the previous year; severe hypertension.
Recruitment/selection of patients	April 2009 to December 2015
Age, gender and ethnicity	Age - Mean (SD): Control 44.5 (17.2); LMWH 47.7 (16.4); Fondaparinux 49.7 (17.3). Gender (M:F): 118/160. Ethnicity: NR
Further population details	1. Active cancer: Not applicable 2. BMI : Mixed (Control 25.1 (3.8); LMWH 26.4 (4.5); Fondaparinux 26.5 (4.1)). 3. Renal impairment: Not applicable 4. Weight bearing: Not applicable
Indirectness of population	No indirectness
Interventions	(n=156) Intervention 1: No treatment - Usual care. Control group - no VTE prophylaxis. Duration for the duration of immobilisation. Mean (SD) 40.3 (8.6) days. Concurrent medication/care: Letter explaining the clinical symptoms associated with the possible development of DVT, PE and side effects of the medication and were asked to contact the ED if any of those occurred. (n=154) Intervention 2: Low molecular weight heparin (not licensed in UK) - Nadroparin (2850 units once daily - up to 57 units/kg once daily). Nadroparin 2850 IE anti/Xa=0/3 ml, given once daily by subcutaneous self-injection. Duration for the duration of immobilisation. Mean (SD) 40.2 (8.5) days. Concurrent medication/care: Letter explaining the clinical symptoms associated with the possible development of DVT, PE and side effects of the medication and were asked to contact the ED if any of those occurred. (n=157) Intervention 3: Fondaparinux - Fondaparinux (all doses). Fondaparinux 2.5mg=0.5ml, given once daily by subcutaneous self-injection. Duration for the duration of immobilisation. Mean (SD) 38.0 (8.7) days. Concurrent medication/care: Letter explaining the clinical symptoms associated with the possible development of DVT, PE and side effects of the medication and were asked to contact the ED if any of those occurred.
Funding	Equipment / drugs provided by industry (Unrestricted educational grant from Glaxo Smith Kline.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NADROPARIN (2850 UNITS ONCE DAILY - UP TO 57 UNITS/KG ONCE DAILY) versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT verified by duplex sonography at duration of immobilisation; Group 1: 2/92, Group 2: 11/94
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 62, Reason: No fracture (5), no plaster cast (18), indication for surgery (9), immobilisation < 4 weeks (5), no sonography (17), withdrew consent (6), other (2); Group 2 Number missing: 62, Reason: No fracture (2), no plaster cast (21), indication for surgery (10), immobilisation < 4 weeks (4), no sonography (23), other (2)

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Symptomatic PE verified by CT angiography at duration of immobilisation; Group 1: 0/92, Group 2: 2/94
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 62, Reason: No fracture (5), no plaster cast (18), indication for surgery (9), immobilisation < 4 weeks (5), no sonography (17), withdrew consent (6), other (2); Group 2 Number missing: 62, Reason: No fracture (2), no plaster cast (21), indication for surgery (10), immobilisation < 4 weeks (4), no sonography (23), other (2)

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding (no definition) at duration of immobilisation; Group 1: 0/92, Group 2: 0/94
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 62, Reason: No fracture (5), no plaster cast (18), indication for surgery (9), immobilisation < 4 weeks (5), no sonography (17), withdrew consent (6), other (2); Group 2 Number missing: 62, Reason: No fracture (2), no plaster cast (21), indication for surgery (10), immobilisation < 4 weeks (4), no sonography (23), other (2)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX (ALL DOSES) versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT verified by duplex sonography at duration of immobilisation; Group 1: 1/92, Group 2: 11/94
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 65, Reason: No fracture (4), no plaster cast (18), indication for surgery (15), immobilisation < 4 weeks (7), no sonography (19), withdrew consent (2); Group 2 Number missing: 62, Reason: No fracture (2), no plaster cast (21), indication for surgery (10), immobilisation < 4 weeks (4), no sonography (23), other (2)

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Symptomatic PE verified by CT angiography at duration of immobilisation; Group 1: 0/92, Group 2: 2/94
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 65, Reason: No fracture (4), no plaster cast (18), indication for surgery (15), immobilisation < 4 weeks

(7), no sonography (19), withdrew consent (2); Group 2 Number missing: 62, Reason: No fracture (2), no plaster cast (21), indication for surgery (10), immobilisation < 4 weeks (4), no sonography (23), other (2)

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding (no definition) at duration of immobilisation; Group 1: 0/92, Group 2: 0/94
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 65, Reason: No fracture (4), no plaster cast (18), indication for surgery (15), immobilisation < 4 weeks (7), no sonography (19), withdrew consent (2); Group 2 Number missing: 62, Reason: No fracture (2), no plaster cast (21), indication for surgery (10), immobilisation < 4 weeks (4), no sonography (23), other (2)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX (ALL DOSES) versus NADROPARIN (2850 UNITS ONCE DAILY - UP TO 57 UNITS/KG ONCE DAILY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT verified by duplex sonography at duration of immobilisation; Group 1: 1/92, Group 2: 2/92
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 65, Reason: No fracture (4), no plaster cast (18), indication for surgery (15), immobilisation < 4 weeks (7), no sonography (19), withdrew consent (2); Group 2 Number missing: 62, Reason: No fracture (5), no plaster cast (18), indication for surgery (9), immobilisation < 4 weeks (5), no sonography (17), withdrew consent (6), other (2)

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Symptomatic PE verified by CT angiography at duration of immobilisation; Group 1: 0/92, Group 2: 9/92
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 65, Reason: No fracture (4), no plaster cast (18), indication for surgery (15), immobilisation < 4 weeks (7), no sonography (19), withdrew consent (2); Group 2 Number missing: 62, Reason: No fracture (5), no plaster cast (18), indication for surgery (9), immobilisation < 4 weeks (5), no sonography (17), withdrew consent (6), other (2)

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding (no definition) at duration of immobilisation; Group 1: 0/92, Group 2: 0/92
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 65, Reason: No fracture (4), no plaster cast (18), indication for surgery (15), immobilisation < 4 weeks (7), no sonography (19), withdrew consent (2); Group 2 Number missing: 62, Reason: No fracture (5), no plaster cast (18), indication for surgery (9), immobilisation < 4 weeks (5), no sonography (17), withdrew consent (6), other (2)	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Unplanned return to theatre at up to 45 days from hospital discharge

Study	**Samama 2013[282]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1349)
Countries and setting	Conducted in Multiple countries; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 45 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	aged ≥18 years, with non-surgical, unilateral single or multiple below-knee injury necessitating rigid or semi-rigid immobilisation (e.g. by plaster cast or brace) for at least 21 days up to 45 days, with at least one additional risk factor for VTE, requiring thromboprophylaxis up to complete mobilisation in investigator's opinion
Exclusion criteria	other traumatic injury
Age, gender and ethnicity	Age - Mean (SD): 46. Gender (M:F): 1:1. Ethnicity: not reported
Further population details	1. Active cancer: No active cancer (0.9% active cancer). 2. BMI: Not obese (BMI under 30 kg/m2) (22.8% BMI >30). 3. Renal impairment: Not stated. 4. Weight bearing: Weight bearing (weight bearing or partial weight bearing (e.g. using crutches, walking cast, or relief shoes)).
Extra comments	plaster cast 83.8%, brace 6.2%, other type of immobilisation 10%

Study	Samama 2013[282]
Indirectness of population	--
Interventions	(n=675) Intervention 1: Fondaparinux - Fondaparinux (all doses). Fondaparinux 2.5mg (or 1.5mg in people with a calculated creatinine clearance between 30-50mL min-1. Duration 21-45 days. Concurrent medication/care: Free to take acetaminophen as needed. Use of aspirin or NSAIDs was allowed but discouraged (n=674) Intervention 2: Low molecular weight heparin (not licensed in UK) - Nadroparin (2850 units once daily - up to 57 units/kg once daily). Nadroparin 2850 units. Duration 21-45 days. Concurrent medication/care: Free to take acetaminophen as needed. Use of aspirin or NSAIDs was allowed but discouraged
Funding	Principal author funded by industry (Abbott, AstraZeneca, Baxter, Bayer, Boehringer-Ingelheim, Bristol Myers-Squibb, CSL Behring, Daichii, Fresenius-Kabi, GlaxoSmithKline, Haemonetics, LFB, Lilly, NovoNordisk, Pfizer, Rovi, Sanofi)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX (ALL DOSES) versus NADROPARIN (2850 UNITS ONCE DAILY - UP TO 57 UNITS/KG ONCE DAILY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 21-45 days; Group 1: 1/621, Group 2: 0/622; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (asymptomatic) confirmed by ultrasongraphy at 21-45 days; Group 1: 11/582, Group 2: 42/585; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE confirmed by pulmonary angiogram at 21-45 days; Group 1: 2/621, Group 2: 0/622; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding: overt and fatal, occurred in a critical organ, was associated with a fall in haemoglobin concentration ≥2g dL-1, or led to a transfusion ≥2 units of packed red blood cells or whole blood at 21-45 days; Group 1: 1/674, Group 2: 0/670; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge

Study	Samama 2013[282]
- Actual outcome: Clinically relevant non-major bleeding: bleeding not qualifying as major, including bleeding leading to treatment discontinuation, gastrointestinal bleeding, haemoptysis, cutaneous hematoma >100cm2, epistaxis >5 minute, recurrent or leading to intervention, spontaneous macroscopic haematuria >24 hour at 21-45 days; Group 1: 1/674, Group 2: 3/670; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: Heparin-induced thrombocytopenia at duration of study - Actual outcome: Thrombocytopenia at 21-45 days; Group 1: 0/674, Group 2: 1/670; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 7: VTE at 7-90 days from hospital discharge - Actual outcome: VTE (any one event) at 21-45 days; Group 1: 14/583, Group 2: 48/586 Protocol outcome 8: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 21-45 days; Group 1: 2/621, Group 2: 7/622 Protocol outcome 9: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (asymptomatic, distal) at 21-45 days; Group 1: 7/582, Group 2: 39/585 - Actual outcome: DVT (symptomatic, distal) at 21-45 days; Group 1: 2/621, Group 2: 5/622 Protocol outcome 10: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (asymptomatic, proximal) at 21-45 days; Group 1: 4/582, Group 2: 3/585 - Actual outcome: DVT (symptomatic, proximal) at 21-45 days; Group 1: 0/621, Group 2: 2/622	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Technical complications of mechanical interventions at duration of study

Study	Selby 2015[294]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=265)
Countries and setting	Conducted in Canada; Setting: 13 Canadian hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 2 weeks + 12 weeks

Study	Selby 2015[294]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 16 years or over with unilateral or bilateral, close or open fractures of the tibia, fibula, or ankle requiring surgical repair
Exclusion criteria	Major trauma; refused study or were unable to consent; presented greater than 72 hours after injury; ongoing need to anticoagulation for other reasons; inability to follow-up; active uncontrolled bleeding; contraindications to contrast due to allergy, pregnancy or renal insufficiency; previous DVT or PE; active cancer; lower extremity vascular injury requiring surgical repair; known systematic bleeding disorder; intracranial or other major bleeding in past 4 weeks; known molecular hypercoagulable state
Recruitment/selection of patients	Between August 2002 and October 2006
Age, gender and ethnicity	Age - Mean (range): 48 (18-87). Gender (M:F): 139:126. Ethnicity: not reported
Further population details	1. Active cancer: No active cancer (excluded). 2. BMI: Not stated. 3. Renal impairment: Not stated. 4. Weight bearing: Not stated.
Extra comments	Immobilisation in cast or splint 98.1%; unilateral fractures 97.4%
Indirectness of population	No indirectness
Interventions	(n=134) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin 5000 units. Duration 2 weeks. Concurrent medication/care: Unilateral or bilateral plaster casts. Aspirin and other antiplatelet agents were allowed if they had been used before the injury for cardiac or stroke prophylaxis. Nonsteroidal anti-inflammatory agents were allowed (n=131) Intervention 2: No treatment - Placebo. Placebo in prefilled syringes. Duration 2 weeks. Concurrent medication/care: Unilateral or bilateral plaster casts. Aspirin and other antiplatelet agents were allowed if they had been used before the injury for cardiac or stroke prophylaxis. Nonsteroidal anti-inflammatory agents were allowed
Funding	Study funded by industry (Canadian Institutes of Health Research-industry partnership with Pfizer Canada)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT, asymptomatic proximal. Confirmed by bilateral Doppler ultrasound at 90 days; Group 1: 1/130, Group 2: 1/128; Risk of bias: High; Indirectness

Study	Selby 2015[294]
of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE, symptomatic. Confirmed by positive spiral computed tomography pulmonary angiogram, high probability V/Q lung scan, or leg imaging at 90 days; Group 1: 0/130, Group 2: 1/128; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding. Defined as overt bleeding that was fatal, life threatening or involved a critical organ or major join, required surgical intervention, transfusion of 1 or more units of blood cells within 48 hours or the bleeding event, or was associated with a drop in haemoglobin of at least 20g/L within 48 hours of the bleeding event at 90 days; Group 1: 0/130, Group 2: 0/128; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Heparin-induced thrombocytopenia at duration of study - Actual outcome: HIT at 90 days; Group 1: 0/130, Group 2: 0/128; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT, symptomatic at 90 days; Group 1: 1/130, Group 2: 1/128	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Technical complications of mechanical interventions at duration of study

H.22 Fragility fractures of the pelvis, hip and proximal femur

Study	Eriksson 2003[97]
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=656)
Countries and setting	Conducted in Argentina, Australia, Belgium, Czech Republic, Denmark, Finland, France, Greece, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom; Setting: 57 centers in 16 countries
Line of therapy	Not applicable
Duration of study	Intervention time: 25-31 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by systemic ascending bilateral contrast venography. PE: confirmed by high-probability lung scanning, pulmonary angiography, spiral computed tomography. Major bleeding: defined as fatal bleeding, retroperitoneal, intracranial, or intraspinal bleeding, bleeding that involved any other critical organ, bleeding leading to reoperation, and overt bleeding with a bleeding index of 2 or more.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged at least 18 years who were undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck, were considered for inclusion if surgery was planned within 48 hours after admission.
Exclusion criteria	Patients were excluded if they presented with trauma affecting more than 1 organ system or if more than 24 hours had elapsed between the causative trauma and hospital admission. Other main exclusion criteria were active bleeding; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; hemorrhagic stroke or brain, spinal, or ophthalmological surgery within the previous 3 months; difficulty in performing epidural or spinal anesthesia; planned indwelling intrathecal or epidural catheter for more than 6 hours after surgery; contraindication to anticoagulant therapy; pregnancy; hypersensitivity to contrast media; or serum creatinine concentration above 2.0 mg/dL (177 µmol/L) in a well-hydrated patient. Patients who required long-term anticoagulant treatment for a chronic comorbid condition or were receiving any type of anticoagulant or fibrinolytic therapy or dextran from admission to first study drug administration or surgery were also excluded.
Recruitment/selection of patients	Between June 2001 and February 2002
Age, gender and ethnicity	Age - Mean (SD): 77 (12) years. Gender (M:F): 1/2. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not obese (BMI under 30 kg/m2) (Median BMI: 25). 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Extra comments	Type of fracture: cervical 41%, trochanteric 52%, subtrochanteric 8%; Median duration of surgery 1 hour 34 minutes; 46% patients used AES
Indirectness of population	No indirectness

Interventions	(n=327) Intervention 1: Fondaparinux - Fondaparinux (all doses). All eligible patients were given a once-daily, subcutaneous injection of 2.5 mg of fondaparinux sodium up to 6-8 days after surgery (standard duration). Patients received a once-daily, subcutaneous injection of 2.5 mg of fondaparinux sodium for 19 to 23 additional days (extended duration), for a total duration of treatment of 25 to 31 days. The first injection was to be given less than 2 hours after randomization. Duration 25-31 days. Concurrent medication/care: Early mobilisation (physiotherapy) recommended. AES permitted. IPCD, dextran, and thrombolytic, anticoagulant, or antiplatelet agents prohibited. Centers were advised to avoid use of aspirin or NSAIDs (n=329) Intervention 2: Fondaparinux - Fondaparinux (all doses). All eligible patients were given a once-daily, subcutaneous injection of 2.5 mg of fondaparinux sodium up to 6-8 days after surgery. Patients receive a once-daily, subcutaneous injection of placebo for 19 to 23 additional days, for a total duration of treatment of 25 to 31 days. The first injection was to be given less than 2 hours after randomization. Duration 25-31 days. Concurrent medication/care: Early mobilisation (physiotherapy) recommended, AES permitted. IPCD, dextran, and thrombolytic, anticoagulant, or antiplatelet agents prohibited. Centers were advised to avoid use of aspirin or NSAIDs
Funding	Study funded by industry (Supported by a grant from Sanofi-Synthelabo, Paris, France and NV Organon, Oss, the Netherlands)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX (EXTENDED DURATION) versus FONDAPARINUX (STANDARD DURATION)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 25-31 days; Group 1: 6/327, Group 2: 8/329
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 25-32 days; Group 1: 3/208, Group 2: 74/218
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 118, Reason: No VTE assessment, inadequate VTE assessment; Group 2 Number missing: 112, Reason: No VTE assessment, inadequate VTE assessment

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 25-31 days; Group 1: 0/326, Group 2: 2/330

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 25-31 days; Group 1: 8/327, Group 2: 2/329 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 25-31 days; Group 1: 0/326, Group 2: 1/330 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: VTE at 7-90 days from hospital discharge - Actual outcome: VTE at 25-31 days; Group 1: 3/208, Group 2: 77/220 Protocol outcome 7: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 25-31 days; Group 1: 1/326, Group 2: 6/330 Protocol outcome 8: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 25-31 days; Group 1: 1/207, Group 2: 42/211 Protocol outcome 9: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 25-31 days; Group 1: 2/221, Group 2: 35/222	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study

Study	**Eskeland 1966[98]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Norway; Setting: Department II, Ulleval Hospital, Norway
Line of therapy	Not applicable
Duration of study	Intervention time: 7-14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted with subcapital or pertrochanteric fracture of the femur
Exclusion criteria	Patients under the age of 56 (anticoagulation considered unnecessary), patients presenting special indications for or contraindications against anticoagulant therapy, patients in whom the effect of anticoagulation prophylaxis could not be evaluated because the guiding principles of the trial could not be followed.
Recruitment/selection of patients	December 1st 1961 to 29th June 1963
Age, gender and ethnicity	Age - Mean (SD): 76 years. Gender (M:F): 1/5. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Extra comments	Type of fracture: subcapital 60%, impacted subcapital 9%, pertrochanteric 40%; mean inpatient stay 25 days
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Vitamin K antagonists - Phenindione (all doses). Phenindione, phenindione therapy was controlled by PP-test or the Thrombotest three times a week until a satisfactory and stable level had been achieved, and then at longer intervals. After an average of five days the PP values had fallen to the level aimed at (below 30% of normal) and there they remained for the rest of the treatment. When the time came to stop the anticoagulant therapy this was done by gradually reducing the dose to zero in the course of one or two weeks. Duration 7-14 days. Concurrent medication/care: Anticoagulant prophylaxis was started on the day of the operation or next day. If the operation was delayed for more than 5 days, and in patients not operated on, prophylactic treatment was started within 5 days of admission. Anticoagulant prophylaxis was started no later than 5 days after the injury. (n=100) Intervention 2: No treatment - Placebo. No anticoagulation prophylaxis received. Duration 7-14 days. Concurrent medication/care: N/A

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENINDIONE (ALL DOSES) versus PLACEBO Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 90 days; Group 1: 19/100, Group 2: 24/100 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 90 days; Group 1: 2/100, Group 2: 6/100 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 90 days; Group 1: 2/100, Group 2: 2/100 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 90 days; Group 1: 1/100, Group 2: 7/100 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of

	study;

Study	**Fisher 1995[102]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=304)
Countries and setting	Conducted in Canada; Setting: Vancouver General Hospital Orthopaedic Trauma Service, Canada
Line of therapy	Not applicable
Duration of study	Intervention time: Mean: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by Doppler ultrasonography PE: confirmed ventilation perfusion (VQ) lung scan
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted with pelvic, acetabular, femoral neck, intertrochanteric, or subtrochanteric fractures. All fractures had to have occurred within the preceding 24 hours.
Exclusion criteria	Abnormal coagulation profile, current or recent use of an antiplatelet or anticoagulation medication, malignancy, severe liver disease, severe vascular disease, skin ulceration or large open wound on lower extremity, objective evidence of DVT, and severe multi-trauma.
Recruitment/selection of patients	Patients admitted between 1st March 1988 and 1st March 1991
Age, gender and ethnicity	Age - Other: >40 years: IPCD group 83%, control group 76%. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=145) Intervention 1: Intermittent pneumatic compression devices - Full leg. Pneumatic sequential leg compression device, applied post-operatively and worn until the patient was ambulating on a routine basis. The IPCD device consisted of a portable controller and a pair of thigh length sleeves. Each sleeve contains six chambers, four calves and two thighs.

	Sleeves are sequentially inflated to pressures of 45 mm Hg at the ankle, 35-40 mm Hg at the calf, and 25 mm Hg at the thigh. The compression cycle was 71 seconds with each compression lasting 11 seconds, this allows for normal refilling of the venous system. Duration Mean: 14 days. Concurrent medication/care: Routine postoperative nursing care and physiotherapy. Included an active mobilisation regimen commencing on postoperative day 1. (n=159) Intervention 2: No treatment - Usual care. Patients received same clinical care as the intervention group. Duration Mean: 13 days. Concurrent medication/care: Routine postoperative nursing care and physiotherapy. Included an active mobilisation regimen commencing on postoperative day 1.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IPCD, THIGH-LENGTH versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at mean: 14 days; Group 1: 9/145, Group 2: 0/159 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 5-10 days; Group 1: 2/145, Group 2: 6/159 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Galasko 1976[113]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention time: Until discharge, transferred or fully mobilised
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT: confirmed by venography PE: confirmed by clinical and radiological examinations or at autopsy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Female patients, over the age of 60 years, who were ambulant before the injury and who had sustained intertrochanteric or transcervical femoral fractures.
Exclusion criteria	Patients under the age of 60, who had a history of DVT, PE, haematemesis, haematuria or other bleeding disorders and patients with malignant disease were excluded from the trial
Recruitment/selection of patients	Based on inclusion criteria
Age, gender and ethnicity	Age - --: Not reported. Gender (M:F): 100% female. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Unfractionated heparin, 5000IU 12 hourly (twice daily), subcutaneously. Duration Until when patients were discharged, transferred or fully mobilised (duration of hospital length of stay not reported) . Concurrent medication/care: Nursing care was identical in both groups as was the postoperative mobilisation. The operative procedure was the same. (n=50) Intervention 2: No treatment - Usual care. Control group. Duration Until when patients were discharged, transferred or fully mobilised (duration of hospital length of stay not reported). Concurrent medication/care: Nursing

	care was identical in both groups as was the postoperative mobilisation. The operative procedure was the same.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at Time-point not reported; Group 1: 15/50, Group 2: 11/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at Time-point not reported; Group 1: 8/50, Group 2: 23/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Time-point not reported; Group 1: 2/50, Group 2: 5/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Infection at duration of study - Actual outcome: Wound infection/haematoma at Time-point not reported; Group 1: 7/50, Group 2: 8/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-

	related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	**Goel 2009[120]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=305)
Countries and setting	Conducted in Canada; Setting: Department of Orthopaedics, University of Calgary, Alberta, Canada
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic) confirmed by bilateral venography Major bleeding: defined as fall in haemoglobin of ≥2 g/dl within a 24-hour period resulting in transfusion of ≥2 units of blood, intracranial, intraspinal, intra-ocular, retroperitoneal or pericardial bleeding, and causing death
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female patients 18-75 years of age, patients with unilateral displaced, fractures below the knee requiring operation, patients with simultaneous injury of a minor nature (e.g. conservatively managed wrist, scapula, clavicular fracture not inhibiting patient mobilisation)
Exclusion criteria	Non-surgical treatment, fractures below the knee, polytrauma patients, fractures not treated within 48 hours, patients with history of DVT or PE, patients limited from early mobilisation, patients with foot fractures, medical contraindications to surgery, patients receiving anticoagulation, inability to provide consent, patients with platelet counts less than 100, patients with elevated serum creatinine > 200µmol/L
Recruitment/selection of patients	December 2000 and July 2006, patients between the ages of 18 and 75 years admitted with unilateral isolated fractures below the knee which required operative fixation
Age, gender and ethnicity	Age - Mean (range): 40.95 years. Gender (M:F): 1.63/1. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Intervention group: mean 27.0; control group mean 26.7). 2. Cancer status: Not applicable 3. Renal impairment: Not applicable

Study	Goel 2009[120]
Extra comments	Type of fracture: tibial plateau 13%, tibial shaft 16%, ankle 63%, pilon, 6.3%, not recorded 1.27%
Indirectness of population	No indirectness
Interventions	(n=157) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Fragmin was administered subcutaneously. 2500IU was administered subcutaneously two hours pre-operatively, followed by 2500IU eight hours post-operatively, and 5000IU on following days each morning up to and including the 14th day. Duration 14 days. Concurrent medication/care: Post-operative rehabilitation was standardised and ward-based physiotherapists directed the patients in early movement exercises. All fractures received a post-operative dressing or immobilisation in a cast depending on the type of fracture. Indirectness: No indirectness (n=148) Intervention 2: No treatment - Placebo. Saline was administered subcutaneously. Placebo (saline) was administered subcutaneously two hours pre-operatively, followed by saline subcutaneous injection eight hours post-operatively, and saline on following days each morning up to and including the 14th day. Duration 14 days. Concurrent medication/care: Post-operative rehabilitation was standardised and ward-based physiotherapists directed the patients in early movement exercises. All fractures received a post-operative dressing or immobilisation in a cast depending on the type of fracture. Indirectness: No indirectness
Funding	Funding not stated (Authors stated in-text that there was a sponsor but no further details reported)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Time-point not reported; Group 1: 1/126, Group 2: 0/111
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 31, Reason: Death, inconclusive venogram, no venogram, negative venogram; Group 2 Number missing: 37, Reason: Death, inconclusive venogram, no venogram, negative venogram

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 14 days; Group 1: 11/126, Group 2: 14/111
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 31, Reason: Death, inconclusive venogram, no venogram, negative venogram; Group 2 Number missing: 37, Reason: Death, inconclusive venogram, no venogram, negative venogram

Study	Goel 2009[120]
Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Time-point not reported; Group 1: 0/126, Group 2: 0/111 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 31, Reason: Death, inconclusive venogram, no venogram, negative venogram; Group 2 Number missing: 37, Reason: Death, inconclusive venogram, no venogram, negative venogram	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Hamilton 1970[135]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=300)
Countries and setting	Conducted in Canada; Setting: Toronto Western Hospital, Canada
Line of therapy	Not applicable
Duration of study	Not clearly reported
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by ascending phlebography
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients admitted with a fracture near the hip
Exclusion criteria	Patients who were not treated by operation, as well as patients with any of the following conditions: recent cerebrovascular accident: diastolic blood pressure of 100 ml of mercury or more: recent head injury; recent peptic ulcer or other gastro-intestinal lesion likely to bleed; recent haemoptysis; recent haematuria; liver disease; renal disease; bleeding diathesis.
Recruitment/selection of patients	Patients admitted between July 1968 and April 1969
Age, gender and ethnicity	Age - Mean (SD): 77 years. Gender (M:F): 1/5. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Vitamin K antagonists - Phenindione (all doses). Phenindione, prothrombin time to two to two and a half times the control was the objective. The level was usually reached by the second day after operation. The prothrombin time was estimated by Quick's one-stage test using Simplastin to compare the patient's plasma with a "Diagnostic Plalsma" control. Duration Unclear. Concurrent medication/care: N/A (n=38) Intervention 2: No treatment - Placebo. Control group, no further details reported. Duration Not clear. Concurrent medication/care: N/A
Funding	Academic or government funding (Support by a grant from Ontario Geriatric Research Society)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENINDIONE (ALL DOSES) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Time-point not reported; Group 1: 4/38, Group 2: 5/38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 5-12 days; Group 1: 10/38, Group 2: 18/37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Time-point not reported; Group 1: 11/38, Group 2: 9/38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Number of units given: VKA group 36 units, control group 22 units; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Infection at duration of study - Actual outcome: Deep wound infection at Time-point not reported; Group 1: 3/38, Group 2: 4/38 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	**Jørgensen 1992[159]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in Denmark; Setting: Department of Orthopaedics, Rigshospitalet, University Hospital, Copenhagen, Denmark
Line of therapy	Not applicable
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by I125 fibrinogen uptake test and scans and ascending phlebography

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted for hip fracture who were 40 years of age or older
Exclusion criteria	Bleeding disorders, hepatic or renal insufficiency, previous septic endocarditis, cerebral hemorrhage during the preceding six months, hypersensitivity to heparin or iodine, and anticoagulant therapy within one week of surgery. Patients from nursing homes were also excluded because they were discharged and returned to recuperate in their nursing homes soon after surgery.
Recruitment/selection of patients	April 1986 to February 1988
Age, gender and ethnicity	Age - Mean (range): 80 years. Gender (M:F): 1/3. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Extra comments	Mean duration of surgery: intervention group (LMWH) 57 minutes, placebo group 60 minutes. Duration of hospitalisation: intervention group (LMWH) 14 days, placebo group 16 days
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Each patient received eight syringes, first and second syringes contained 2500IU and subsequent ones contained 5000IU. Injections were given subcutaneously. The first injection was administered two hours preoperatively and the second injection 12 hours postoperatively. The remaining six injections were given once each morning on the six following days. Duration 7 days. Concurrent medication/care: N/A (n=38) Intervention 2: No treatment - Placebo. The control group received placebo injections following the same schedule used by the LMWH group. Duration 7 days. Concurrent medication/care: N/A
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 84 days; Group 1: 3/30, Group 2: 4/38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

	Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 9 days; Group 1: 9/30, Group 2: 22/38 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 84 days; Group 1: 0/30, Group 2: 1/38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Infection at duration of study - Actual outcome: Superficial wound infection at 84 days; Group 1: 2/30, Group 2: 2/38 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	**Lahnborg 1980[183]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=140)

Countries and setting	Conducted in Sweden; Setting: Serafimerlasarettet (Seraphim Hospital), Stockholm, Sweden
Line of therapy	Not applicable
Duration of study	Intervention time: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by I125 fibrinogen uptake test and scans
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted for nailing of a fractured neck of the femur, no history of venous thrombosis or pulmonary embolism during two years before the trial, no patients received oral anticoagulants for a previous thromboembolism.
Exclusion criteria	None reported
Recruitment/selection of patients	Consecutive patients admitted for nailing of a fractured neck of the femur.
Age, gender and ethnicity	Age - Mean (range): 77 (39-97) years. Gender (M:F): 1/2. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Extra comments	Mean duration of surgery, 122 minutes
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Sodium heparin was given at a dosage of 5000 units subcutaneously into the thigh every 12 hours for 10 days, starting 2-3 hours before the operation. Duration 10 days. Concurrent medication/care: N/A (n=69) Intervention 2: No treatment - Placebo. Placebo, 0.5ml of 0.85% saline was given every 12 hours for 10 days starting 2-3 hours before the operation. Duration 10 days. Concurrent medication/care: N/A
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 10 days; Group 1: 15/71, Group 2: 28/69

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Time-point not reported; Group 1: 2/71, Group 2: 0/69 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	**Monreal 1989[229]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Spain; Setting: Orthopaedic Surgery and Roentgenology, Hospital de Badalona, Barcelona, Spain
Line of therapy	Not applicable
Duration of study	Intervention time: 9 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: PE: confirmed by ventilation-perfusion lung scanning
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients admitted because of hip fracture and over 40 years of age, all of them operated on the day of fracture.
Exclusion criteria	Patients with underlying bleeding disorder
Recruitment/selection of patients	Based on inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): 77 (11) years. Gender (M:F): 1/5. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Extra comments	Duration of operation: mean 93 minutes
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). LMWH, Kabi 2165 (dalteparin) was obtained in 0.2ml prefilled syringes with a potency of 2500IU and 5000IU. 2500IU was given 2 hours before surgery and then 5000IU subcutaneously every morning for 9 days. To observe the same injection schedule as in the UFH group, a placebo was given in the evening doses (patients received injections every 8 hours). Duration 9 days. Concurrent medication/care: Early mobilisation encouraged, it was planned to have all patients sit on the second day and stand up before the first week ended. (n=44) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH, 5000IU was given subcutaneously 2 hours before operation, and then at 8 hour intervals for the next 9 days. Duration 9 days. Concurrent medication/care: Early mobilisation encouraged, it was planned to have all patients sit on the second day and stand up before the first week ended.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN versus UNFRACTIONATED HEPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Time-point not reported; Group 1: 2/46, Group 2: 3/44
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 8 days; Group 1: 6/46, Group 2: 0/44

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at Time-point not reported; Group 1: 14/46, Group 2: 6/44	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	**Morris 1976[230]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in United Kingdom; Setting: Nottingham General Hospital, Nottingham
Line of therapy	Not applicable
Duration of study	Intervention time: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by I125 fibrinogen uptake test and scans PE: confirmed by clinical signs, chest X-rays, and electrocardiograms
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	Patient aged 60 or over, the diagnosis of fractured neck of femur (subcapital or intertrochanteric) had been confirmed and there were no grounds for exclusion from the trial
Exclusion criteria	Prothrombin index of less than 70%, a severe unexplained anemia or bleeding tendency; active peptic ulceration; malignant hypertension; renal failure; liver disease; pathological fracture; recent stroke or severe intellectual impairment; clinical evidence of venous thrombosis.
Recruitment/selection of patients	During a 12 month period all patients aged 60 years and over who were admitted to Nottingham General Hospital with a fracture of the femoral neck were considered for entry into the trial.
Age, gender and ethnicity	Age - Mean (SD): 78.3 years. Gender (M:F): 1/7. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Extra comments	Site of hip fracture: subcapital 52%; pertochanteric 48%
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Vitamin K antagonists - Warfarin (all doses). Oral warfarin sodium was given to the treatment group, treatment being controlled by the 'Thrombotest' method, using venous blood-samples. A thrombotest level of 10% was aimed for to achieve modest degree of anticoagulation. All patients received an oral loading dose of 30mg of warfarin sodium within 24 hours of admission. No warfarin was given on the next day. On the 3rd day a thrombotest level was obtained, and the next dose of warfarin was prescribed according to the result. Duration Until independently mobilised or 3 months. Concurrent medication/care: All patients were given routine ward physiotherapy before and after operation. (n=80) Intervention 2: No treatment - Usual care. Control group were not treated. No further details reported. Duration Until independently mobilised or 3 months. Concurrent medication/care: All patients were given routine ward physiotherapy before and after operation.
Funding	Study funded by industry (Study was supported by a grant from Boehringer Ingelheim Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN (ALL DOSES) versus CONTROL GROUP

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Time-point not reported; Group 1: 16/80, Group 2: 23/80
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 10 days; Group 1: 23/75, Group 2: 50/74 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Failure in supply of fibrinogen; Group 2 Number missing: 6, Reason: Failure in supply of fibrinogen Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Time-point not reported; Group 1: 0/80, Group 2: 2/80 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Time-point not reported; Group 1: 8/80, Group 2: 2/80 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	**Moskovitz 1978[231]**
Study type	RCT (randomised; Parallel)

Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in USA; Setting: The George Washington University Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by I125 fibrinogen uptake test and scans PE: confirmed by radionuclide perfusion lung-scanning
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted with diagnosis of hip fracture.
Exclusion criteria	Prior history of VTE, a history of gastric or duodenal ulcer with haemorrhage within the previous six months, a positive stool guaiac (2+ or greater), haematuria, a sensitivity to iodinated compounds, or a diastolic blood pressure greater than 110 ml of mercury. Other reasons for exclusion were a patient's refusal to be involved in the study and technical problems and errors either in the collection of data in the conduct of the protocol.
Recruitment/selection of patients	Based on inclusion criteria
Age, gender and ethnicity	Age - Other: 61% ≥70 years. Gender (M:F): 1/2. Ethnicity: 43% White
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Renal impairment (eGFR less than 30 ml/min/1.73m2) (Renal stasis: 50% patients in each treatment group).
Indirectness of population	--
Interventions	(n=29) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH, 5000IU administered subcutaneously every 8 hours, first dose was given at 6am, 2pm or 10pm. All patients wore AES. Duration 7 days. Concurrent medication/care: Early mobilisation was encouraged, patients were required to stand at the bedside on the first or second postoperative day and then permitted to transfer with assistance from the bed to a char. They were allowed to stand and walk with assistance and external support on the second postoperative day, as tolerated. (n=23) Intervention 2: No treatment - Placebo. Placebo (saline) administered subcutaneously every 8 hours, first dose was given at 6am, 2pm or 10pm. All patients wore AES. Duration 7 days. Concurrent medication/care: Early mobilisation was encouraged, patients were required to stand at the bedside on the first or second postoperative day and then permitted to transfer with assistance from the bed to a char. They were allowed to stand and walk with assistance and

	external support on the second postoperative day, as tolerated.
Funding	Academic or government funding (Grant from the National Heart and Lung Institute of the National Institutes of Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN + AES versus PLACEBO + AES

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Time-point not reported; Group 1: 0/29, Group 2: 3/23
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 10 days; Group 1: 10/29, Group 2: 8/23
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Time-point not reported; Group 1: 2/29, Group 2: 1/23
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at Time-point not reported; Group 1: 0/29, Group 2: 0/23
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at Time-point not reported; Group 1: 0/29, Group 2: 1/23
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	**PENTHIFRA trial: Eriksson 2001[93]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1711)
Countries and setting	Conducted in Argentina, Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Netherlands, New Zealand, Norway, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, United Kingdom; Setting: 99 centers in 21 countries
Line of therapy	Not applicable
Duration of study	Intervention time: 5-9 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by systemic ascending bilateral contrast venography. PE: confirmed by high-probability lung scanning, pulmonary angiography, helical computed tomography. Major bleeding: defined as fatal bleeding, retroperitoneal, intracranial, or intraspinal bleeding, bleeding that involved any other critical organ, bleeding leading to reoperation, and overt bleeding with a bleeding index of 2 or more.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged at least 18 years who were undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck, were considered for inclusion if surgery was planned within 48 hours after admission.
Exclusion criteria	Patients were excluded if they presented with trauma affecting more than 1 organ system or if more than 24 hours had elapsed between the causative trauma and hospital admission. Other main exclusion criteria were active bleeding; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; hemorrhagic stroke or brain, spinal, or ophthalmological surgery within the previous 3 months; difficulty in performing epidural or spinal anesthesia; planned indwelling intrathecal or epidural catheter for more than 6 hours after surgery;

	contraindication to anticoagulant therapy; pregnancy; hypersensitivity to contrast media; or serum creatinine concentration above 2.0 mg/dL (177 µmol/L) in a well-hydrated patient. Patients who required long-term anticoagulant treatment for a chronic comorbid condition or were receiving any type of anticoagulant or fibrinolytic therapy or dextran from admission to first study drug administration or surgery were also excluded.
Recruitment/selection of patients	November 1998 to October 1999
Age, gender and ethnicity	Age - Mean (SD): 77 (12.5) years. Gender (M:F): 1/3. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI: 24). 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Extra comments	Type of fracture: cervical 47%, trochanteric 44%, subtrochanteric 8%; Median duration of surgery 103 minutes; 49% patients used AES
Indirectness of population	No indirectness
Interventions	(n=862) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Patients were assigned to receive once-daily subcutaneous injections of 40 mg enoxaparin and a placebo. In the enoxaparin group, the first active dose was given 12±2 hours preoperatively and the second 12 to 24 hours postoperatively. Treatment was scheduled to continue until day 5 to day 9. Duration 5-9 days. Concurrent medication/care: Early mobilisation (physiotherapy) recommended. AES permitted. IPCD, dextran, and thrombolytic, anticoagulant, or antiplatelet agents prohibited. Centers were advised to avoid use of aspirin or NSAIDs (n=849) Intervention 2: Fondaparinux - Fondaparinux (all doses). Patients were assigned to receive once-daily subcutaneous injections of 2.5 mg of fondaparinux and a placebo. The first dose of fondaparinux was administered 6±2 hours postoperatively and the second 12 hours or more after the first. Treatment was scheduled to continue until day 5 to day 9. Duration 5-9 days. Concurrent medication/care: Early mobilisation (physiotherapy) recommended. AES permitted. IPCD, dextran, and thrombolytic, anticoagulant, or antiplatelet agents prohibited. Centers were advised to avoid use of aspirin or NSAIDs
Funding	Study funded by industry (Supported by a grant from Sanofi-Synthelabo, Paris, France and NV Organon, Oss, the Netherlands)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LMWH (STANDARD DOSE) versus FONDAPARINUX

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 49 days; Group 1: 42/842, Group 2: 38/831
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death; Group 2 Number missing: 18, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 11 days; Group 1: 117/623, Group 2: 49/624
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 239, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death; Group 2 Number missing: 225, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 11 days; Group 1: 1/831, Group 2: 1/840
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death; Group 2 Number missing: 9, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 11 days; Group 1: 19/842, Group 2: 18/831
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death; Group 2 Number missing: 18, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death

Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 11 days; Group 1: 2/840, Group 2: 2/831
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death; Group 2 Number missing: 18, Reason: Inclusion criteria not met, technical problems, withdrawn consent, death

Protocol outcome 6: VTE at 7-90 days from hospital discharge
- Actual outcome: VTE at 11 days; Group 1: 119/624, Group 2: 52/626

Protocol outcome 7: DVT (symptomatic) at 7-90 days from hospital discharge

- Actual outcome: DVT (symptomatic) at 11 days; Group 1: 1/840, Group 2: 1/831 Protocol outcome 8: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 11 days; Group 1: 94/626, Group 2: 42/627 Protocol outcome 9: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 11 days; Group 1: 28/646, Group 2: 6/650	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	**PEP Trial trial: Pulmonary embolism prevention (pep) trial collaborative group 2000[269]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=13356)
Countries and setting	Conducted in Australia, New Zealand, South Africa, Sweden, United Kingdom; Setting: 152 hospitals across 5 countries
Line of therapy	Not applicable
Duration of study	Intervention time: 35 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: PE: confirmed by pulmonary angiogram, a high-probability ventilation-perfusion scan and at necropsy. Fatal PE: confirmed by necropsy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a femoral-neck fracture or other fracture of the proximal femur.
Exclusion criteria	Patients with clear indication for aspirin (such as a recent myocardial infarction, or clear contraindication to aspirin (such as an active peptic ulcer)
Recruitment/selection of patients	Between March 1992 and July 1998

Age, gender and ethnicity	Age - Mean (SD): 79 years. Gender (M:F): 1/4. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Cancer status: Not applicable 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=6679) Intervention 1: Aspirin - Aspirin (up to 300mg). Aspirin, 160 mg, orally, once daily [plus adjuvant pharmacological and mechanical prophylaxis]. Duration 35 days. Concurrent medication/care: 44% also UFH or LMWH and 30% also using TED stockings (n=6677) Intervention 2: No treatment - Placebo. Placebo, orally, once daily [plus adjuvant pharmacological and mechanical prophylaxis]. Duration 35 days. Concurrent medication/care: 43% also UFH or LMWH and 29% also using TED stockings. Serious indirectness (combination outcome, not no prophyslaxis).
Funding	Academic or government funding (Study funded by the Health Research Council of New Zealand, the National Heart Foundation of New Zealand, the Wishbone Trust of New Zealand, the Auckland Orthopaedic Society, the National Health and Medical Council of Australia, and the British Heart Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 35 days; Group 1: 447/6679, Group 2: 461/6677
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 35 days; Group 1: 28/6679, Group 2: 38/6677
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 35 days; Group 1: 18/6679, Group 2: 43/6677
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Infection at duration of study - Actual outcome: Wound infection with frank pus at 35 days; Group 1: 98/6679, Group 2: 84/6677 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 35 days; Group 1: 69/6679, Group 2: 97/6677	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	**Svend-hansen 1981[309]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=130)
Countries and setting	Conducted in Denmark; Setting: Department of Orthopaedic Surgery, Copenhagen County Hospital, Glostrup. Denmark.
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by I125 fibrinogen uptake test and scans, this was completed daily.
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients with proximal femoral fractures
Exclusion criteria	Patients: under 20 years of age, with coagulation disorders, with a previous history of DVT or PE, with an active malignant disease, receiving oral anticoagulants or heparin, receiving salicylates, admitted later than 6 hours after fracture. Pregnant women.
Recruitment/selection of patients	Patients with proximal femoral fractures from 3rd January 1977 until the 18th January 1979
Age, gender and ethnicity	Age - Mean (range): 73 years . Gender (M:F): 1/3. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=65) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Patients received 5000 units of heparin, three times a day for 14 days, i.e. until mobilisation. The first injection was given as soon as the patients were admitted to hospital. Duration 14 days. Concurrent medication/care: N/A (n=65) Intervention 2: No treatment - Placebo. Placebo given three times daily (no further details reported), until mobilisation. Duration 14 days. Concurrent medication/care: N/A
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Time-point not reported; Group 1: 15/65, Group 2: 6/65
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 14 days; Group 1: 15/65, Group 2: 28/65
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge

- Actual outcome: Fatal PE at Time-point not reported; Group 1: 1/65, Group 2: 1/65 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	**Tang 2017[311]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=287)
Countries and setting	Conducted in China; Setting: Orthopaedics Department of the Second Affiliated Hospital of Xi'an Jiaotong University
Line of therapy	Not applicable
Duration of study	Intervention time: 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: PE: confirmed by CT pulmonary angiogram (CTPA) when PE was suspected and/or confirmed.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Fractures that were caused by fall-induced damage, the patients who were admitted to the hospital within 24 hours following injury, the patients who were diagnosed by X-ray and/or CT, and all patients who received internal fixation.
Exclusion criteria	Lower extremity DVT that was confirmed preoperative imaging, the patients who had a history of thromboembolic

	disease and were undergoing anticoagulant therapy, the patients with haemorrphagic diseases and/or major bleeding history (such as intracranial haemorrhage or gastrointestinal bleeding that required blood transfusion), the patients with coagulation disorders and/or contraindications to anticoagulation and the patients who were contraindicated to rivaroxaban and/or LMWH.
Recruitment/selection of patients	Patients with hip fracture that were admitted to the Orthopaedics Department of the Second Affiliated Hospital of Xi'an Jiaotong University from September 2011 to September 2016.
Age, gender and ethnicity	Age - Mean (SD): 70 years. Gender (M:F): 1/1.6. Ethnicity: Not reported
Further population details	1. Below knee: Not applicable 2. BMI : Not obese (BMI under 30 kg/m2) (BMI (mean): 23.5). 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Extra comments	Fracture site: femoral neck fracture 57.8%, intertrochanteric fracture of the femur 42.2%.
Indirectness of population	No indirectness
Interventions	(n=96) Intervention 1: Rivaroxaban - Rivaroxaban (all doses). Rivaroxaban (10mg) was administered orally from 6 hours following operation. Duration 28 days. Concurrent medication/care: All patients underwent rehydration, analgesic actions, anti-infection, and correction of anaemia. Patients were encouraged to perform passive movement training of the affected limbs at day 2 after the surgery. Indirectness: No indirectness (n=95) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin (40mg/4000IU) was administered once daily from 12 hours following the operation. Duration Duration of LMWH unclear (assumption that it was for 28 days). Concurrent medication/care: All patients underwent rehydration, analgesic actions, anti-infection, and correction of anaemia. Patients were encouraged to perform passive movement training of the affected limbs at day 2 after the surgery. Indirectness: Serious indirectness (n=96) Intervention 3: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin (40mg/4000IU) was administered once daily from 12 hours following the operation for one week. Rivaroxaban (10mg) was administered orally once daily for 28 days . Duration LMWH (1 week), rivaroxaban (28 days) . Concurrent medication/care: All patients underwent rehydration, analgesic actions, anti-infection, and correction of anaemia. Patients were encouraged to perform passive movement training of the affected limbs at day 2 after the surgery. Indirectness: No indirectness
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (EXTENDED DURATION) versus RIVAROXABAN	

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 30 days; Group 1: 1/95, Group 2: 0/96
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 30 days; Group 1: 12/95, Group 2: 5/96
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Study did not seem to screen all patients for DVT using confirmation technique of Colour Doppler ultrasound. Doppler ultrasound was recommended for asymptomatic patients. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 30 days; Group 1: 2/95, Group 2: 1/96
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 30 days; Group 1: 1/95, Group 2: 0/96
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: VTE at 7-90 days from hospital discharge
- Actual outcome: VTE at 30 days; Group 1: 14/95, Group 2: 5/96

Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge
- Actual outcome: DVT (distal) at 30 days; Group 1: 4/95, Group 2: 2/96

Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge
- Actual outcome: DVT (proximal) at 30 days; Group 1: 6/96, Group 2: 3/96

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN + RIVAROXABAN versus RIVAROXABAN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge

- Actual outcome: All-cause mortality at 30 days;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 30 days; Group 1: 9/96, Group 2: 5/96
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Study did not seem to screen all patients for DVT using confirmation technique of Colour Doppler ultrasound. Doppler ultrasound was recommended for asymptomatic patients. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 30 days; Group 1: 1/96, Group 2: 1/96
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 30 days; Group 1: 1/96, Group 2: 0/96
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: VTE at 7-90 days from hospital discharge
- Actual outcome: VTE at 30 days; Group 1: 10/96, Group 2: 5/96

Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge
- Actual outcome: DVT (distal) at 30 days; Group 1: 3/96, Group 2: 2/96

Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge
- Actual outcome: DVT (proximal) at 30 days; Group 1: 6/96, Group 2: 3/96

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN + RIVAROXABAN versus ENOXAPARIN (EXTENDED DURATION)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 30 days;

	Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 30 days; Group 1: 9/96, Group 2: 12/95 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Study did not seem to screen all patients for DVT using confirmation technique of Colour Doppler ultrasound. Doppler ultrasound was recommended for asymptomatic patients. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 30 days; Group 1: 1/96, Group 2: 2/95 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 30 days; Group 1: 1/96, Group 2: 1/95 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: VTE at 7-90 days from hospital discharge - Actual outcome: VTE at 30 days; Group 1: 10/96, Group 2: 14/95 Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 30 days; Group 1: 3/96, Group 2: 4/95 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 30 days; Group 1: 6/96, Group 2: 8/95 Risk of bias: All domain - ; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital

	discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study; D

Study	**Xabregas 1978[344]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Australia; Setting: Prince of Wales Hospital Accident Centre
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed I125 fibrinogen test
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a fractured neck of the femur.
Exclusion criteria	Not reported
Recruitment/selection of patients	Between July 1975 and April 1976
Age, gender and ethnicity	Age - Mean (SD): 75.6 years (1.5). Gender (M:F): 1/3. Ethnicity: Not reported
Further population details	1. Immobilisation: Not applicable 2. BMI : Not applicable 3. Cancer status: Not applicable 4. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Calcium heparin, prophylactic treatment commenced as soon as possible after the patient's admission to hospital, each patient receiving 0.01 ml/kg body weight of the solution in the ampoule subcutaneously every 8 hours. This volume represented 100 IU/kg heparin every eight hours in the treated group, the treatment was continued in each patient for a total period of 2 weeks. Duration 14 days. Concurrent medication/care: N/A

	(n=25) Intervention 2: No treatment - Placebo. Placebo, saline solution. Duration 14 days. Concurrent medication/care: N/A
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at Time-point not reported; Group 1: 4/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Time-point not reported; Group 1: 2/25, Group 2: 0/25
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Infection at duration of study
- Actual outcome: Wound infection at Time-point not reported; Group 1: 2/25, Group 2: 2/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

H.23 Elective hip replacement

Study	EPCAT trial: Anderson 2013[7]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=786)
Countries and setting	Conducted in Canada; Setting: Tertiary care (orthopaedic referral centres)
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 28 days + Follow-up 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Described in two related but separate articles.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients undergoing elective unilateral THA at the participating institutions (12 university-affiliated hospitals in Canada)
Exclusion criteria	Hip fracture in past 3 months; metastatic cancer; life expectancy < 6 months; bleeding that precluded use of anticoagulant prophylaxis; active peptic ulcerdisease / gastritis that precluded aspirin use; aspirin allergy; heparin-induced thrombocytopenia / heparin allergy; creatinine clearance < 30mL/min per 1.73m²; platelet count < 100 x 10^9 cells/L; need for long-term anticoagulation due to a pre-existing comorbid condition / VTE developing after surgery but before randomisation; unwillingness/inability to give informed consent
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Dalteparin 57.9 (12.2) vs. Aspirin 57.6 (11.9). Gender (M:F): 444:341. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness: Ethnic composition of the participants is not reported.
Interventions	(n=400) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Further course of 5000U of subcutaneous dalteparin injections once daily started between 8 and 10 days after surgery (i.e. after the run-in period). Duration 28 days. Concurrent medication/care: Run-in period for all participants: began in the morning after surgery with 5000U of subcutaneous dalteparin injections once daily for 10

Study	EPCAT trial: Anderson 2013[7]
	days. Concomitant treatment: oral placebo tablets to mimic aspirin, given at the same time as dalteparin. (n=386) Intervention 2: Aspirin - Aspirin (up to 300mg). Oral aspirin tablets 81mg once daily. Duration 28 days. Concurrent medication/care: Run-in period for all participants: began in the morning after surgery with 5000U of subcutaneous dalteparin injections once daily for 10 days. Concomitant treatment: subcutaneous placebo injections to mimic dalteparin, given at the same time as aspirin.
Funding	Academic or government funding (Canadian Institutes of Health Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN versus ASPIRIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death at 90 days; Group 1: 1/400, Group 2: 0/385
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - During the study, a novel oral anticoagulant, rivaroxaban, was approved in Canada and this had a major effect on the recruitment of the participants so the committee deemed that the study completion was no longer feasible, and after an interim analysis the committee decided to terminate recruitment after 786 patients had been randomly assigned.; Indirectness of outcome: No indirectness ; Baseline details: Ethnicity is not reported.; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: One participant failed to sign the consent form after randomisation.

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 90 days; Group 1: 3/398, Group 2: 0/380
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Refer to outcome "Death" for early termination of the trial.; Indirectness of outcome: No indirectness ; Baseline details: Ethnicity is not reported.; Group 1 Number missing: 2, Reason: Two participants withdrew consent.; Group 2 Number missing: 6, Reason: One participant failed to sign the consent form after randomisation. Five participants withdrew consent.

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 90 days; Group 1: 1/400, Group 2: 0/385; Comments: Difference (95% CI) = 0.25 (-4.9 to 1.0); p=1.00
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Refer to outcome "Death" for early termination of the trial.; Indirectness of outcome: No indirectness ; Baseline details: Ethnicity is not reported.; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: One participant failed to sign the consent form after randomisation.

Study	EPCAT trial: Anderson 2013[7]
	Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 90 days; Group 1: 0/400, Group 2: 0/385 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Refer to outcome "Death" for early termination of the trial.; Indirectness of outcome: No indirectness ; Baseline details: Ethnicity is not reported.; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: One participant failed to sign the consent form after randomisation. Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically significant non-major bleeding at 90 days; Group 1: 4/400, Group 2: 2/385; Comments: Difference (95% CI) = 0.48 (-1.0) to 2.0); p=0.68 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Refer to outcome "Death" for early termination of the trial.; Indirectness of outcome: No indirectness ; Baseline details: Ethnicity is not reported.; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: One participant failed to sign the consent form after randomisation. Protocol outcome 6: Infection at duration of study - Actual outcome: Wound infection at 90 days; Group 1: 10/400, Group 2: 12/385; Comments: p=0.67 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Refer to outcome "Death" for early termination of the trial.; Indirectness of outcome: No indirectness ; Baseline details: Ethnicity is not reported.; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: One participant failed to sign the consent form after randomisation. Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Symptomatic proximal DVT in the leg at 90 days; Group 1: 2/398, Group 2: 1/380 Protocol outcome 8: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Surgical site of bleeding at 90 days; Group 1: 5/400, Group 2: 4/386
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Avikainen 1995 [9]	RCT	1+	Total: 167 Intervention: n = 83 (DVT assessed in 79) Control: n = 84 (DVT assessed in 79)	Type of surgery: Hip replacement (& Duration of surgery)	Type: LMWH (Enoxaparin) Dose: 40mg/0.4 ml	Type: UFH Dose: 5000 IU	Both groups: Until discharge (10th post- op -).	DVT Confirmed by: US on 10-14th post-op day.	US results for 158 patients Int: 1/79 Control: 4/79 p value: >0.05	Also reported: perioperative and postoperative blood loss, transfusion requirements Not reported: PTS, QoL, survival, LoS, funding
				Intervention: Mean age: 65 (range 27-86) years M/F:30/53	Timing: Begun 12hrs pre-op and repeated daily for 10 days Additional non-comparative prophylaxis: Not reported	Timing: Begun 2hrs pre-op and repeated twice daily for 10 days		PVT Confirmed by: US on 10-14th post-op day.	Int: 1/79 Control: 4/79 p value: >0.05	
				Control: Mean age: 66 (range 34-86) M/F:25/59				PE Confirmed by: Not routinely assessed. Symptomatic confirmed by V/Q scan	All patients: Int: 0/84 Control: 1/83 p value: 0.4970	
				Pre-existing risk factors: varicose veins						

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bailey 1991[13]	RCT	1+	Total 95 Int: 50	Type of surgery: total hip replacement Mean operating time Int: 184.5	sequential pneumatic compression device covering legs and thighs	low dose warfarin Dose: 10mg	Control: 5 to 7 days (also day	DVT Confirmed by: venography (see comments)	Int: 3/50 Control: 12/45 p value: <0.006 (significant)	Weight was significantly greater in the warfarin group to the

			Cont: 45	min Cont: 208.5 min Intervention: Mean age: 65.3 (range: 41-88) yrs M/F:24/26 Control: Mean age: 64.4 (range: 45-50) M/F:22/23	Timing: Applied after surgery in the recovery ward and worn continuously for the remainder of the study (except during bathing and physical therapy). Additional non-comparative prophylaxis: AES applied on admission and continued until after discharge.	before surgery (7.5mg for women over 70 and patients with minor abnormalities of liver function tests). Timing: Evening before surgery and doses given after surgery adjusted to maintain a prothrombin time at 14-16 seconds. Prothrombin times routinely obtained by postoperative day 2 or 3. Additional non-comparative prophylaxis: AES applied before and after surgery	diagnostic test done for DVT) Int: 5 to 7 days (also day diagnostic test done for DVT)	Clinically relevant non-major bleeding (defined in the paper as "clinically important bleeding")	Int: 0/50 Control: 0/45 p value: N/A	sequential compression group. There was no significant difference in weight between groups for those who developed DVT. Diagnosis of DVT for those where there was a lack of venous access: B- mode Doppler US and technecium-pyrophosphate red-cell labelled nuclear venogram with impedance plethysmography. Funding: Kendall Inc supplied the stockings (not under investigation). Unclear whether they

										provided any other support/materials

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bergqvist 1996 [22]	RCT	1+	Total: 262 Intervention n: 131 Control n: 131	Type of surgery: Patients scheduled for Total hip replacement surgery. Surgery was performed expeditiously with a mean duration of 1.9 hours (range 1.0 to 5.0). Intervention: Mean age: 70 (range: 44 - 87 years) M/F:56/75 Control: Mean age: 70 (Range: 44 – 87 years) M/F:57/	Type, dose and timing: 40 mg of Enoxaparin injected subcutaneously into abdomen once daily. The first active dose was given 12±2 hrs preoperatively until day 21 Additional non-comparative prophylaxis: Not reported	Type, dose and timing: Placebo or Single dose of 0.4 ml saline.	3 months	DVT confirmed by bilateral ascending phlebography	Int: 21/117 Control: 43/116 p value: 0.0012	
								PE Confirmed by ventilation – perfusion lung scan or a pulmonary angiography.	Int: 0/117 Control: 2/116 p value: 0.2468	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				74 Pre-existing risk factors: Previous VTE: Int: n = 8 Control: n = 12 Varicose veins: Int: n = 27 Control: n = 31 Leg ulcer: Int: n = 2 Control: n = 3						

Study	Bern 2015[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=118)
Countries and setting	Conducted in USA; Setting: New England Baptist Hospital, Boston, USA
Line of therapy	Not applicable
Duration of study	Intervention time: 26-30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by bilateral duplex

Study	Bern 2015[28]
	sonography PE: confirmed by ventilation/perfusion lung scan or computerised axial tomography angiogram
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were recruited from among over 20 years of age planning elective primary unilateral total hip or knee replacement surgery at an orthopaedic surgery.
Exclusion criteria	Abnormal platelet count, prothombin time or partial thromboplastin time; surgery for acute fracture (<4 weeks), septic joint, or extraction athroplasty; history of VTE or documented hypercoagulation syndrome; increased risk of haemorrphage, as from active gastric ulcer or urinary tract bleed within the last year; haemorrphagic stroke, brain, spinal, or ophthalmologic surgery in previous 6 months; liver enzymes or bilirubin greater than 2 x normal; decreased renal function with GFR <30 ml/min; cancer in last year, other than localised cancers of the skin; requires chronic anticoagulation; requires chronic platelet function suppressive therapy; prior adverse reaction to any of the study drugs; uncontrolled hypertension; BMI >42, pregnancy
Recruitment/selection of patients	Based on inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): 63 (8.2) years. Gender (M:F): 1/1. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=64) Intervention 1: Fondaparinux - Fondaparinux (all doses). 2.5mg daily starting 6 or more hours following surgery, but no later than 6am the next day, or 6-8 hours after epidural catheter removal. All patients wore pneumatic compression stockings while in-patient. AES were prescribed to be used after discharge until the follow-up ultrasounds. Duration 28±2 days. Concurrent medication/care: Use of platelet function suppressive drugs, such a non-steroidal anti-inflammatory drugs (NSAIDs), was discouraged but not prohibited by the protocol. (n=54) Intervention 2: Vitamin K antagonists - Warfarin (all doses). 5.0mg beginning the night before surgery, followed by 5.0mg the PM of surgery, and then variable daily dose (target INR 2.0-2.5). All patients wore pneumatic compression stockings while in-patient. AES were prescribed to be used after discharge until the follow-up ultrasounds. Duration 28±2 days. Concurrent medication/care: Use of platelet function suppressive drugs, such a non-steroidal anti-inflammatory drugs (NSAIDs), was discouraged but not prohibited by the protocol.
Funding	Funding not stated

Study	Bern 2015[28]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX + IPCD + AES versus WARFARIN + IPCD + AES Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 28±2 days; Group 1: 0/64, Group 2: 0/54 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 28±2 days; Group 1: 0/64, Group 2: 0/54 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 28±2 days; Group 1: 0/64, Group 2: 0/54 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 28±2 days; Group 1: 0/64, Group 2: 0/54 Protocol outcome 5: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 28±2 days; Group 1: 0/64, Group 2: 0/54	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study;

Study	Bern 2015[28]
	Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Cohen 2007[62]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=856)
Countries and setting	Conducted in Brazil, Hong Kong (China), Spain, United Kingdom; Setting: Brazil, UK, Hong Kong and Spain
Line of therapy	Not applicable
Duration of study	Intervention time: Fondaparinux 5-9 days; AES 35-49 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Venous thromboembolism was defined by at least one of the following: objectively verified, symptomatic thromboembolism (proximal or distal DVT or fatal or non-fatal pulmonary embolism), or asymptomatic proximal DVT demonstrated by bilateral proximal ultrasound or venography.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Minimum age 18 years, primary or revision total hip replacement, surgery for fracture of the proximal third of the femur.
Exclusion criteria	Bilateral joint surgery, multiple trauma, delay > 24 hours between trauma and admission, conditions precluding use of AES, leg oedema, peripheral vascular disease, peripheral neuropathy, marked leg deformity, conditions that increase the risk of bleeding, pregnant/lactating women or those of child bearing age taking inadequate contraceptive precautions.
Recruitment/selection of patients	Between January 2002 and November 2004, patients were recruited from Brazil, UK, Hong Kong and Spain.
Age, gender and ethnicity	Age - Mean (range): 65 years (18-99). Gender (M:F): 1/1.32. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI 28 (range: 15-50.1)). 2. Renal impairment: Not applicable
Extra comments	History of VTE: 12%. 96% of patients had elective total hip replacement, 5% standard fracture surgery. This study was previously included in the hip fracture evidence review in the guideline (CG92).
Indirectness of population	No indirectness
Interventions	(n=426) Intervention 1: Fondaparinux - Fondaparinux (all doses). Fondaparinux (2.5 mg daily) for five to nine days. The first dose of fondaparinux was given six hours after closure of the surgical wound and the second dose 18 to 24 hours later. Subsequent doses were administered daily at a median interval of 22 to 26 hours for between five and nine days. Duration 5-9 days. Concurrent medication/care: N/A

Study	Cohen 2007[62]
	(n=430) Intervention 2: Fondaparinux - Fondaparinux (all doses). Fondaparinux (2.5 mg daily) for five to nine days plus AES for 35 to 49 days. The first dose of fondaparinux was given six hours after closure of the surgical wound and the second dose 18 to 24 hours later. Subsequent doses were administered daily at a median interval of 22 to 26 hours for between five and nine days. Long-leg stockings were used unless the thigh circumference necessitated the use of short-leg stockings. The stockings were applied pre-operatively and worn until the last follow-up visit (35-49 days). Duration total of 35-49 days. Concurrent medication/care: N/A
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX + AES versus FONDAPARINUX

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 35-49 days; Group 1: 1/391, Group 2: 3/404
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 39, Reason: withdrew consent, did not meet all the early criteria, postponed surgery for six months or cancelled surgery, had symptomatic venous thromboembolism, the investigator decided not to randomise them, or there was a pharmacy error.; Group 2 Number missing: 22, Reason: withdrew consent, did not meet all the early criteria, postponed surgery for six months or cancelled surgery, had symptomatic venous thromboembolism, the investigator decided not to randomise them, or there was a pharmacy error.

Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 35-49 days; Group 1: 0/391, Group 2: 1/404
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 39, Reason: withdrew consent, did not meet all the early criteria, postponed surgery for six months or cancelled surgery, had symptomatic venous thromboembolism, the investigator decided not to randomise them, or there was a pharmacy error.; Group 2 Number missing: 22, Reason: withdrew consent, did not meet all the early criteria, postponed surgery for six months or cancelled surgery, had symptomatic venous thromboembolism, the investigator decided not to randomise them, or there was a pharmacy error.

Protocol outcome 3: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 35-49 days; Group 1: 0/391, Group 2: 0/404
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Study	Cohen 2007[62]
Indirectness of outcome: No indirectness ; Group 1 Number missing: 39, Reason: withdrew consent, did not meet all the early criteria, postponed surgery for six months or cancelled surgery, had symptomatic venous thromboembolism, the investigator decided not to randomise them, or there was a pharmacy error.; Group 2 Number missing: 22, Reason: withdrew consent, did not meet all the early criteria, postponed surgery for six months or cancelled surgery, had symptomatic venous thromboembolism, the investigator decided not to randomise them, or there was a pharmacy error. Protocol outcome 4: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding at 35-49 days; Group 1: 16/391, Group 2: 20/404 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 39, Reason: withdrew consent, did not meet all the early criteria, postponed surgery for six months or cancelled surgery, had symptomatic venous thromboembolism, the investigator decided not to randomise them, or there was a pharmacy error.; Group 2 Number missing: 22, Reason: withdrew consent, did not meet all the early criteria, postponed surgery for six months or cancelled surgery, had symptomatic venous thromboembolism, the investigator decided not to randomise them, or there was a pharmacy error.	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Colwell 1994[68]	Multicent re RCT	1+	Total: 610 Multicentre study	Type of surgery: Hip replacement surgery, including primary and	Int A: Enoxaparin 30mg every 12 hours	Int B: Enoxaparin 40mg once daily	Study period: 7 days	DVT Confirmed by: bilateral contrast venography	Int A: 8 (n = 136) Int B: 28 (n = 136) Int C: 21 (n = 142)	Comments: Only 67.9% of patients evaluated for DVT.

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			involving 32 institutions Int A: 195 In B: 203 Int C: 209	revision procedures, in patients 40 years or older					p value not reported	Multicentre study, not all centres used a valid diagnostic technique (same numbers in each group). An intention to treat analysis was followed. Results are available for patients diagnosed by valid test alone as well as all patients.
						Int C: 5000 units UFH every 8 hours		Proximal DVT Confirmed by: bilateral contrast venography	Int A: 4 (n = 136) Int B: 8 (n = 136) Int C: 10 (n = 142) p value not reported	
				Intervention A: Mean age: 65.6±10.97 yrs M/F:98/97	Timing: Administered within 24 hours after surgery and continued for a maximum of 7 days.	Timing: Administered within 24 hours after surgery and continued for a maximum of 7 days.		Distal DVT Confirmed by: bilateral contrast venography	Int A: 4 (n = 136) Int B: 20 (n = 136) Int C: 11 (n = 142) p value not reported	
				Intervention B: Mean age: 65.0±11.31 yrs M/F:99/104				PEs (symptomatic) (not reported how confirmed)	Int A: 0 (n = 195) Int B: 1 (n = 203) Int C: 4 (n = 209) p value: not reported	
				Intervention C: Mean age: 65.6±10.65 yrs M/F:101/108	Additional non-comparative prophylaxis: No. patients receiving epidural/spinal anaesthesia: Int A: 64/195	Additional non-comparative prophylaxis: No. patients receiving epidural/spinal anaesthesia:		Major bleeding episodes	Int A: 8 (n = 195) Int B: 3 (n = 203) Int C: 13 (n = 209) p value: not reported	Other outcomes reported: Total proximal and distal DVTs (i.e. confirmed by venography, supportive
				Pre-existing risk factors:				Moderate thrombocyto	Int A:7 (n = 195) Int B: 3 (n = 203)	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				Excluded patients include: a history of DVT, PE or both and heparin associated thrombocytopenia.		Int B: 72/203 Int C: 72/209		penia episodes (20x109/L to 100x109/L. In no case was the count <50x109/L).	Int C: 5 (n = 209) p value: not reported	non- invasive vascular examinations or other clinical evidence of treatment failure.) haemoglobin levels, minor bleeding
								Mortality during study not due to sudden death by PE	Int A: 1 (n = 136) Int B: 0 (n = 136) Int C: 2 (n = 142) p value not reported	
								Adverse events (no. of patients, none completed the study)	Int A: 7 (n = 136) Int B: 5 (n = 136) Int C: 12 (n = 142) p value not reported	Not reported: PEs in hospital PTS, QoL,
								No. of patients rehospitalised (due to symptomatic DVT or PE).	Int A: 3 (n = 136) Int B: 1 (n = 136) Int C: 4 (n = 142) p value not reported	Funding: Rhone Poulenc Pharmaceuticals

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Colwell 1999 [66]	RCT	1+	Total: 3011 Intervention: n = 1495 Control: n = 1516	Type of surgery: Elective total hip arthroplasty Intervention: Mean age: 64.1±13.21 (range: 19-99) M/F:659/836 Control: Mean age: 63.9±13.7 yrs (range: 18-100) M/F: 678/838 Pre-existing risk factors: Significantly more obese patients in enoxoparin arm Int: 378/1376 had BMI >30kg/m2 (27.5%) (BMI reported for	Type: Coumadin (adjusted dose warfarin) Dose: Started at 7.5mg, adjusted to maintain INR ratio between 2.0 to 3.0 Timing: Started between 48 hours preoperatively (at the discretion of the investigator) and 24 hours postoperatively. Administered until discharge. Additional non-comparative prophylaxis:	Type: Enoxoparin (LMWH) Dose: 30mg Timing: Every 12 hours, started within 24 hours post-operatively once haemostasis (cessation of active bleeding as determined by the investigator) had been established Administered until discharge.	Both groups: 14 days treatment, 3 month follow up	Symptomatic DVT Confirmed by US or venography	Int: 44/1495 Control: 40/1506 p value: 0.6592	Comments: Results not stratified by BMI. No of VTEs by BMI: BMI >30 = 48/111 (43.2%) BMI <30 = 63/111 (56.8%) No of VTEs out of total no. of BMI group BMI >30 = 48/837 (5.73%) BMI <30 = 63/1959 (3.22%) Also reported: Minor bleeding Not reported: PTS, LoS, QoL, fatal PE
								Symptomatic DVT that occurred in hospital	Int: 15/1495 Control: 2/1506 p value: 0.0012	
								Symptomatic DVT that occurred after discharge	Int: 29/1495 Control: 38/1506 p value: 0.3232	
								PE Confirmed by ventilation perfusion scan or pulmonary angiography	Int: 9/1495 Control: 6/1506 p value: 0.4518	
								PE that occurred in hospital	Int: 2/1495 Control: 1/1506 p value: 0.6235	
								PE that occurred after discharge	Int: 7/1495 Control: 5/1506 p value: 0.5789	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				92% of this group) Control: 459/1420 had >30kg/m2 (32.3%) (BMI reported for 93.7% of this group) p = 0.0055	Stockings permitted but not reported how many patients received these	Additional non-comparative prophylaxis: Stockings permitted but not reported how many patients received these		Both DVT & PE Confirmed by one of the above methods	Int: 3/1495 Control: 9/1506 p value: 0.1452	Funding: No direct funding for this study. Indirect funding (i.e. authors' institution funding) Rhone Poulenc Rorer Pharmaceuticals
								Both DVT & PE that occurred in hospital	Int: 0/1495 Control: 1/1506 p value: 1.0000	
								Both DVT & PE that occurred after discharge	Int: 3/1495 Control: 8/1506 p value: 0.2257	
								Major bleeds	Int: 4/1495 Control:6/1516 p value: 0.2658	
								Adverse events (most commonly reported were fever, anaemia, nausea)	Int: 934/1495 Control: 987/1506 p value: 0.0870	
								Serious adverse events	Int: 134/1495 Control: 167/1506 p value: 0.0128	
								Survival	Int: 1485/1495	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								(specify)	Control: 1497/1506 p value: 0.8226	

Study	Comp 2001[71]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=435)
Countries and setting	Conducted in USA; Setting: Multicentre trial
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 29 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing elective hip replacement who gave written consent
Exclusion criteria	Patients undergoing multiple joint replacement or in whom hemostasis was not achieved within 12-24 hours after surgery. Patients treated with hip replacement who had undergone surgery on the ipsilateral hip in the preceding 6 months, the ipsilateral knee or contralateral knee within the previous three months. Clinical evidence of chronic or acute DVT; a history of venous thromboembolic disease within 12 months before the surgery; generalised haemorrhagic diathesis or hypercoagulable syndrome; a documented allergy to UFH or a history of heparin associated thrombocytopenia; a skin rash or necrosis; allergy to fish or swine products, iodine, or radiopaque contrast medium; current drug or alcohol abuse; surgery on the eye, spinal cord or central nervous system; documented stroke or myocardial infarction within one month before entry into the study; active ulcerative disease or angiodysplasia of the gastrointestinal tract; active gastrointestinal bleeding within the last 6 months; uncontrolled hypertensin; use of aspirin-containing products or NSAID agents daily within the four days preceding hospitalisation; receipt of another investigational drug within the preceding 4 weeks; and clinically relevant diseases or treatments that could interfere with the study medications or their evaluation.
Recruitment/selection of patients	Not reported

Study	Comp 2001[71]
Age, gender and ethnicity	Age - Mean (SD): LMWH extd 64.4 (28-90); LMWH std 63.4 (26-88). Gender (M:F): 1:!. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI: LMWH ext 28.4 (16.1-53.7); LMWH std 28.5 (16.6-45)). 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=224) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin, high dose, extended duration (30mg twice daily). Enoxaparin treatment was initiated 12-24 hours postoperatively and continued for 7-10 days. Patients were then administered 40mg once daily subcutaneously for 3 weeks. Duration 28-31 days. Concurrent medication/care: Not reported (n=211) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin, high dose, extended duration (30mg twice daily). Enoxaparin treatment was initiated 12-24 hours postoperatively and continued for 7-10 days. Patients were then administered saline solution once daily subcutaneously for 3 weeks. Duration 28-31 days. Concurrent medication/care: Not reported
Funding	Study funded by industry (Funds were received in total or partial support of the research from Aventis Pharmaceuticals Incorporated, Bridgewater, New Jersey and Aventis Pharma SA Antony, France)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) EXTENDED versus ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) STANDARD

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 29 days; Group 1: 15/152, Group 2: 39/138
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 72; Group 2 Number missing: 73

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 29 days; Group 1: 0/224, Group 2: 1/211
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial,

Study	Comp 2001[71]
intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 29 days; Group 1: 0/224, Group 2: 0/211 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: CRNMB at 29 days; Group 1: 2/224, Group 2: 5/211 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Heparin-induced thrombocytopenia at duration of study - Actual outcome: Thrombocytopenia at 29 days; Group 1: 3/224, Group 2: 2/211 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 29 days; Group 1: 10/152, Group 2: 19/138 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 29 days; Group 1: 5/152, Group 2: 20/138	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Dahl 1997[75]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=227)

Study	Dahl 1997[75]
Countries and setting	Conducted in Norway; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 35 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female patients (over 18 years of age), who were admitted to hospital for elective primary or secondary arthroplasty of the hip (arthrosis, femoral neck fracture sequela) and from whom written consent was obtained
Exclusion criteria	Patients with known renal or liver insufficiency, cerebral bleeding less than 3 months before surgery, or known haemorrhagic diathesis, eye or ear surgery within 1 month before surgery, severe hypertension, septic endocarditis, threatened arterial circulation in the leg, a body weight less than 40kg, anticoagulant therapy less than 1 week before surgery, a known hypersensitivity to heparin, LMWH, dextran or contrast media, pregnancy or breast feeding, inability to comply with the study protocol, and previous surgery in this study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 70.9; placebo group: 71.4. Gender (M:F): 1:2.4. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=117) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin, 5000IU once daily (standard dose), subcutaneously given from the evening before the operation until 4 weeks after. Below-knee AES was also used, on both legs before the operation and for the first post-operative week. Duration 4 weeks. Concurrent medication/care: n/a (n=110) Intervention 2: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin, 5000IU once daily (standard dose), subcutaneously administered from the evening before the operation until 7 days after then administered placebo (sodium chlordie) in the evenings. Below-knee AES was also used, on both legs before the operation and for the first post-operative week. Duration 7 days. Concurrent medication/care: n/a
Funding	Funding not stated

Study	Dahl 1997[75]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (EXTENDED DURATION) + AES versus DALTEPARIN (STANDARD DURATION) + AES Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 35 days; Group 1: 22/114, Group 2: 33/104 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 6 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 35 days; Group 1: 0/111, Group 2: 3/106 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 6	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Eriksson 1991[92]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=LMWH: 67; Unfractionated heparin: 69)
Countries and setting	Conducted in Sweden; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10-14 days

Study	Eriksson 1991[92]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by bilateral ascending phlebography. PE confirmed by pulmonary perfusion scintigraphy.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who were 40 years or older and had been admitted consecutively for elective total hip replacement.
Exclusion criteria	People with a history of bleeding disorders, liver or renal disease, cerebral hemorrhage within 6 months before the time of the study, ongoing anticoagulant therapy, hypersensitivity to heparin or iodine, or previous inclusion in the study.
Recruitment/selection of patients	People admitted for total hip replacement between November 1987 and May 1989 were allocated randomly to either treatment group.
Age, gender and ethnicity	Age - Mean (SD): LMWH: 68.4 (8.2); Unfractionated heparin: 69.0 (8.0). Gender (M:F): LMWH: 26/40; Unfractionated heparin: 30/39. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=67) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 5000 IU once daily (standard dose) subcutaneously from the evening before the operation until 10 days post-operation. Placebo was also given twice daily. Duration 10-14 days. Concurrent medication/care: Mobilisation and physiotherapy started on the first day after the operation (n=69) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000 IU three times daily, subcutaneously from two hours pre-operation for 10 days. Placebo was only given on the pre-operative evening. Duration 10-14 days. Concurrent medication/care: Mobilisation and physiotherapy started on the first day after the operation
Funding	Academic or government funding (Grants from the Swedish Medical Research Council, Project 00660; the Medical Society of Gothenburg; and Gothenburg University.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler)

Study	Eriksson 1991[92]
ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 12-14 days; Group 1: 19/63, Group 2: 25/59 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 10 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 12-14 days; Group 1: 1/67, Group 2: 2/69 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding (definition not reported) at 10 days; Group 1: 1/67, Group 2: 5/69 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Haematoma > 0.5cm at site of injection at Not reported; Group 1: 2/67, Group 2: 7/68 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Heparin-induced thrombocytopenia at duration of study - Actual outcome: Heparin-induced thrombocytopenia at Not reported; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT distal at 12-14 days; Group 1: 12/63, Group 2: 4/59 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at 12-14 days; Group 1: 7/63, Group 2: 21/59	

Study	Eriksson 1991[92]
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	RENOVATE I trial: Eriksson 2007[91]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=Dabigatran etexilate 220mg: 1146; Dabigatran etexilate 150mg: 1163; Enoxaparin: 1154)
Countries and setting	Conducted in Australia, South Africa; Setting: 115 centres in Europe, Australia, and South Africa.
Line of therapy	Not applicable
Duration of study	Intervention time: 28-35 days (treatment time included the time from first dose to 3 days after the last dose of the study drug)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was confirmed by by a consistent intraluminal filling defect on at least two venogram images. PE was established by ventilation-perfusion scintigraphy, pulmonary angiography, spiral chest CT, or by autopsy. Symptomatic DVT was confirmed by compression ultrasound or venography.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18 years or older, weighing at least 40kg, who were scheduled for primary elective unilateral total hip replacement, were eligible for enrolment.
Exclusion criteria	Any bleeding diathesis; history of acute intracranial disease or haemorrhagic stroke; major surgery, trauma, uncontrolled hypertension, or myocardial infarction in the past 3 months; gastrointestinal or urogenital bleeding, or ulcer disease in the past 6 months; severe liver disease; alanine or aspartate aminotransferase concentrations greater than two times the upper limit of the normal range in the past month; severe renal insufficiency (creatinine clearance less than 30ml/min); use of long-acting non-steroidal anti-inflammatory drugs (also contraindicated during treatmnet); childbearing potential; allergy to radiopaque contrast media or heparin; and active malignant disease.
Recruitment/selection of patients	Not reported

Study	RENOVATE I trial: Eriksson 2007[91]
Age, gender and ethnicity	Age - Mean (SD): Dabigatran etexilate 220mg: 65 (10); Dabigatran etexilate 150mg: 63 (11); Enoxaparin: 64 (11). Gender (M:F): Sex (female) - Dabigatran etexilate 220mg: 636 (56%); Dabigatran etexilate 150mg: 667 (57%); Enoxaparin: 651 (56%). Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=1146) Intervention 1: Dabigatran - Dabigatran (all doses). 220mg once daily orally (started 1-4 hours after surgery with a half dose of 110mg) . Duration 28-35 days. Concurrent medication/care: Concomitant administration of low dose aspirin (less than 160mg) and selective cyclo-oxygenase-2 inhibitors was allowed during treatment. AES were also permitted. (n=1154) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 40mg (standard dose) subcutaneously once a day (Sanofi-Aventis), administered from the evening before the operation. Duration 28-35 days. Concurrent medication/care: Concomitant administration of low dose aspirin (less than 160mg) and selective cyclo-oxygenase-2 inhibitors was allowed during treatment. AES were also permitted.
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DABIGATRAN (ALL DOSES) versus ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death at 28-35 days; Group 1: 3/1137, Group 2: 3/1156
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 12

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: Total asymptomatic and symptomatic deep-vein thrombosis at 28-35 days; Group 1: 45/880, Group 2: 57/897; Comments: Dabigatran: 45/880 Enoxaparin: 57/897
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 266; Group 2 Number missing: 257
- Actual outcome: Proximal asymptomatic deep-vein thrombosis at 28-35 days; Group 1: 18/905, Group 2: 32/914
- Actual outcome: Distal asymptomatic deep-vein thrombosis at 28-35 days; Group 1: 22/874, Group 2: 24/894

Study	RENOVATE I trial: Eriksson 2007[91]
	Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: Symptomatic PE at 28-35 days; Group 1: 5/880, Group 2: 3/897 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 12 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 28-35 days; Group 1: 23/1146, Group 2: 18/1154 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding at 28-35 days; Group 1: 48/1146, Group 2: 40/1154 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: Symptomatic deep-vein thrombosis at 28-35 days; Group 1: 6/1137, Group 2: 1/1142
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	RECORD1 trial: Eriksson 2008[94]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=4541)

Study	RECORD1 trial: Eriksson 2008[94]
Countries and setting	Conducted in Multiple countries; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 35 days + Follow-up maximum of 35 days after last dose of study drug
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was assessed using systematic ascending, bilateral venography. Suspected PE was confirmed using spiral computed tomography, perfusion-ventilation lung scintigraphy or pulmonary angiography. Autopsies were requested for deaths.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18 years or older who were scheduled to undergo elective total hip arthroplasty
Exclusion criteria	Scheduled for staged bilateral hip arthroplasty; pregnancy/breastfeeding; active bleeding / high risk of bleeding; contraindication for prophylaxis with enoxaparin or a condition that might require an adjusted dose of enoxaparin; conditions preventing bilateral venography; substantial liver disease; severe renal impairment (creatinine clearance < 30ml/min); concomitant use of protease inhibitors for HIV infection; planned intermittent pneumatic compression; requirement for anticoagulant therapy that could not be stopped
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): Rivaroxaban 63.1 (18-91) vs. Enoxaparin 63.3 (18-93). Gender (M:F): 1971:2462. Ethnicity: White 92.3%; Hispanic 1.2%; Black 0.9%; Asian 0.2%; Other/Missing 5.5%
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=2266) Intervention 1: Rivaroxaban - Rivaroxaban (all doses). Oral 10mg tablets once daily, started 6 to 8 hrs after wound closure. Duration 35 days. Concurrent medication/care: Placebo injections to match enoxaparin injections, given at the same time as rivaroxaban (n=2275) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous injections 40mg once daily, started 12 hrs before surgery and restarted 6 to 8 hrs after wound closure. Duration 35 days. Concurrent medication/care: Placebo tablets to match rivaroxaban, given at the same time as enoxaparin
Funding	Study funded by industry (Bayer HealthCare and Johnson & Johnson)

Study	RECORD1 trial: Eriksson 2008[94]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN versus ENOXAPARIN Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: Death during treatment period at 35 days after surgery; Group 1: 4/1595, Group 2: 4/1558; Comments: ARR 0.0 (95% CI -0.4 to 0.4); p=1.00 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 671, Reason: 57 did not receive a study drug + 17 did not undergo planned surgery + 1 received wrong study drug + 588 had inadequate assessment of thromboembolism + 8 had inadequate evaluation of efficacy; Group 2 Number missing: 717, Reason: 51 did not receive a study drug + 21 did not undergo planned surgery + 635 had inadequate assessment of thromboembolism + 8 had inadequate evaluation of efficacy - Actual outcome: Death during follow-up period at Up to 35 days after last dose of study drug; Group 1: 1/1595, Group 2: 0/1558; Comments: ARR 0.1 (95% CI-0.2 to 0.4); p=1.00 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 671, Reason: 57 did not receive a study drug + 17 did not undergo planned surgery + 1 received wrong study drug + 588 had inadequate assessment of thromboembolism + 8 had inadequate evaluation of efficacy; Group 2 Number missing: 717, Reason: 51 did not receive a study drug + 21 did not undergo planned surgery + 635 had inadequate assessment of thromboembolism + 8 had inadequate evaluation of efficacy Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 35 days after surgery; Group 1: 12/1595, Group 2: 53/1558; Comments: ARR -2.7 (95% CI-3.7 to -1.7); p<0.001 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 671, Reason: 57 did not receive a study drug + 17 did not undergo planned surgery + 1 received wrong study drug + 588 had inadequate assessment of thromboembolism + 8 had inadequate evaluation of efficacy; Group 2 Number missing: 717, Reason: 51 did not receive a study drug + 21 did not undergo planned surgery + 635 had inadequate assessment of thromboembolism + 8 had inadequate evaluation of efficacy Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: Non-fatal PE during treatment period at 35 days after surgery; Group 1: 4/1595, Group 2: 1/1558; Comments: ARR 0.2 (95% CI -0.1 to 0.6); p=0.37 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: It does not include fatal PE.; Group 1 Number missing: 671, Reason: 57 did not receive a study drug + 17 did not undergo planned surgery + 1 received wrong study drug + 588 had inadequate assessment of thromboembolism + 8 had inadequate evaluation of efficacy; Group 2 Number missing: 717, Reason: 51 did not receive a study drug + 21 did not undergo planned surgery + 635 had inadequate assessment of thromboembolism + 8 had inadequate evaluation of efficacy	

Study	RECORD1 trial: Eriksson 2008[94]
Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Between the first dose of study drug and up to 2 days after the last dose; Group 1: 40/2266, Group 2: 33/2275; Comments: p=0.18 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 57, Reason: 57 participants did not receive any study drug; Group 2 Number missing: 51, Reason: 51 participants did not receive any study drug Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding at Between the first dose of study drug and up to 2 days after the last dose; Group 1: 65/2209, Group 2: 54/2224 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 57, Reason: 57 participants did not receive any study drug; Group 2 Number missing: 51, Reason: 51 participants did not receive any study drug Protocol outcome 6: Infection at duration of study - Actual outcome: Post-operative wound infection at Between the first dose of study drug and up to 2 days after the last dose; Group 1: 8/2209, Group 2: 8/2224 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 57, Reason: 57 participants did not receive any study drug; Group 2 Number missing: 51, Reason: 51 participants did not receive any study drug Protocol outcome 7: VTE at 7-90 days from hospital discharge - Actual outcome: Major VTE during treatment period at 35 days after surgery; Group 1: 4/1686, Group 2: 4/1678; Comments: ARR -1.7 (95% CI -2.5 to -1.0); p<0.001 Protocol outcome 8: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at Between the first dose of study drug and up to 2 days after the last dose; Group 1: 1/2209, Group 2: 0/2224; Comments: The single fatal bleeding case occurred before the administration of the first dose of rivaroxaban.	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven

Study	Eriksson 2011[95]

Study	Eriksson 2011[95]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2013)
Countries and setting	Conducted in Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Hungary, India, Italy, Netherlands, New Zealand, Norway, Poland, South Africa, Spain, Sweden, USA; Setting: 108 centres in 19 countries. Geographical location: Western Europe 51%, Central Europe 18%, North America 16.8%, India 8.9%, Australia/New Zealand/South Africa 5%
Line of therapy	Not applicable
Duration of study	Intervention time: 28-35 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by ascending, bilateral venography using a modification of the Rabinov and Paulin technique. PE: confirmed by ventilation-perfusion scintigraphy and chest X-ray, pulmonary angiography, spiral chest computer tomography or by autopsy. Major bleeding: defined as a bleeding event that meets at least one of the following criteria: fatal bleeding, critical bleeding (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, in a non-operated joint, or intramuscular with compartment syndrome, clinically overt bleeding (at surgical or extra-surgical site) associated with a decrease in the haemoglobin level of more than 2 g/dL (20 g/l; 1.24 mmol/L), clinically overt bleeding (at surgical or extra-surgical site) leading to transfusion of two or more units of whole blood or packed cells, bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (e.g. draining or puncture of an haematoma at the surgical site, transfer to an ICU or emergency room) [taken from European Medicines Agency guideline] Clinically relevant non-major bleeding: defined as any clinically overt bleeding that does not meet the criteria for major bleeding but requires medical attention (e.g. hospitalisation, medical treatment for bleeding) and/or change in antithrombotic therapy (including discontinuation or down-titration of study drug) and/or any other bleeding type considered to have clinical consequences for a patient. [taken from European Medicines Agency guideline]
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men or women aged 18 years or older and scheduled for primary, unilateral, elective total hip arthroplasty were eligible for inclusion.
Exclusion criteria	Those with bleeding-related contraindications, contraindications to enoxaparin or dabigatran treatment; elevated liver enzymes (alanine aminotransferase level [ALT] greater than three times the upper limit of the normal range [ULN]).

Study	Eriksson 2011[95]
Recruitment/selection of patients	Patients recruited between March 2008 and May 2009
Age, gender and ethnicity	Age - Mean (SD): 62 (12) years. Gender (M:F): 1/1. Ethnicity: 90.4% White; 8.9% Asian; 0.3% Black; Other 0.5%
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI for both arms: 27.8 ±4.8). 2. Renal impairment: Not
Extra comments	Duration of surgery (mean median time in minutes): 80 minutes; History of DVT or PE: 2.5%
Indirectness of population	No indirectness
Interventions	(n=1019) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin, 40mg subcutaneous injections once daily with a placebo of the other study drug. Subcutaneous treatment was started the evening before surgery (some countries started post-operatively to reflect local practice). The first oral dose was halved (placebo capsule) and given 1-4 hours after completion of surgery. Duration 28-35 days. Concurrent medication/care: If dosage was contraindicated on the day of surgery (e.g. the patient was not hemodynamically stable), a full dose of placebo was started the morning after surgery. (n=1036) Intervention 2: Dabigatran - Dabigatran (all doses). Dabigatran orally given (2x 110mg capsules), together with a placebo of the other study drug. Subcutaneous treatment was started the evening before surgery (some countries started post-operatively to reflect local practice) (placebo). The first oral dose was halved (one capsule 110mg) and given 1-4 hours after completion of surgery. Duration 28-25 days. Concurrent medication/care: If dosage was contraindicated on the day of surgery (e.g. the patient was not hemodynamically stable), a full dose of dabigatran (220mg) was started the morning after surgery.
Funding	Funding not stated (Funding for the study not reported - disclosure of fees received by authors as a consultant or speaker for pharmaceutical companies, including AstraZeneca, Bayer, Boehringer Ingelheim and GlaxoSmithKline.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (40MG ONCE DAILY) versus DABIGATRAN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 28-35 days; Group 1: 1/992, Group 2: 0/1001
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: Not treated, did not undergo surgery; Group 2 Number missing: 35, Reason: Not treated, did not undergo surgery

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge

Study	Eriksson 2011[95]
- Actual outcome: DVT (symptomatic and asymptomatic) at 28-35 days; Group 1: 67/783, Group 2: 60/791 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 236, Reason: Not treated, did not undergo surgery, venography not performed; Group 2 Number missing: 245, Reason: Not treated, did not undergo surgery, venography not performed Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE (symptomatic non-fatal) at 28-35 days; Group 1: 2/992, Group 2: 1/1001 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: Not treated, did not undergo surgery; Group 2 Number missing: 35, Reason: Not treated, did not undergo surgery Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 28-35 days; Group 1: 9/1003, Group 2: 14/1010 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 16, Reason: Not treated, did not undergo surgery; Group 2 Number missing: 26, Reason: Not treated, did not undergo surgery Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding at 28-35 days; Group 1: 20/1003, Group 2: 23/1010 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 16, Reason: Not treated, did not undergo surgery; Group 2 Number missing: 26, Reason: Not treated, did not undergo surgery Protocol outcome 6: VTE at 7-90 days from hospital discharge - Actual outcome: Symptomatic VTE at 28-35 days; Group 1: 6/992, Group 2: 1/1001 Protocol outcome 7: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 28-35 days; Group 1: 4/992, Group 2: 0/1001 Protocol outcome 8: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 28-35 days; Group 1: 35/785, Group 2: 43/792

Study	Eriksson 2011[95]
Protocol outcome 9: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 28-35 days; Group 1: 31/792, Group 2: 17/804	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Fordyce 1992[104]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=79)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6-9 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with osteoarthritis undergoing primary total hip replacement
Exclusion criteria	Refused venogram, venogram not possible, death
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Foot pump + AES group 68.1; AES group 71.2. Gender (M:F): 1:1.7. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Foot pumps or foot impulse devices - Foot pumps. Foot pump, A-V Impulse System, an inflatable pad is placed under the foot, held in place by a slipper and connected to an air-impulse generator that provides rapid inflation and deflation for 3 seconds, cycle repeated every 20 seconds. Fitted to the foot of the operated limb, and using whenever the patient was in bed or sitting at rest. AES was also applied to both legs.

Study	Fordyce 1992[104]
	. Duration Unclear. Concurrent medication/care: Patients practiced active leg exercises and were mobilised on the second postoperative day (n=40) Intervention 2: Anti-embolism stockings - Mixed above/below knee. Control group, AES on both legs alone. Duration Unclear. Concurrent medication/care: Patients practiced active leg exercises and were mobilised on the second postoperative day
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOOT PUMP + AES versus AES ALONE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 6-9 days; Group 1: 4/39, Group 2: 16/40 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Francis 1992[105]	RCT	1+	Total: Intervention : n = 98 Control: n = 103	Type of surgery: Orthopaedic Total hip replacement Duration of surgery not reported Intervention: Mean age: 64±12 yrs M/F:43/55 Control: Mean age: 64±5 M/F:52/51 Pre-existing risk factors: 13 patients (Int 7, control 6 - Not significant difference) had prior history of VTE	Type: bilateral thigh- calf IPCD Dose: 35-55 mm Hg Timing: applied immediately prior to surgery. Continued until venography (6-8 day post-op). Additional non-comparative prophylaxis: bilateral thigh-high AES. Patients moved from bed to chair on 2nd day post-op, began ambulation and physical therapy on 3rd day post-op	Type: Warfarin Dose: low intensity regimen, adjusted to achieve INR of 1.5 on day of surgery, and 2.5 post-operatively Timing: Begun 10 -14 days pre-operatively. Continued until venography (6-8 day post-op). Additional non-comparative prophylaxis: bilateral thigh-high AES. Patients moved from bed to chair	Intervention until venography (on average around day 9)	DVT Confirmed by: Venography 6-8 days post-op. Bilateral: Int. 87, control. 84. Operated-on leg only: int.11, control 19	Int: 26/98 Control: 32/103 p value: 0.5346	Comments: Of the initial 232 patients randomised, 220 received prophylaxis (all assessed for bleeding/arterial thrombotic complications), 201 were assessed for DVT with venography. Overall incidence of deep calf vein (distal) thrombi significantly lower in IPCD group. Not reported: PE, Fatal PE, PTS, QoL:
								Proximal DVT Confirmed by: venography (as above).	Int: 12/98 Control: 3/103 p value: <0.012	
								Length of Hospital Stay	Mean LoS 9 days (s.d. not reported). LoS not reported separately for each group	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
						on 2nd day post- op, began ambulation and physical therapy on 3rd day post-op				

Study	Francis 1997[106]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=550)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 9 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by bilateral ascending venography. Major bleeding defined as fatal or if the patient required a transfusion, a reoperation or prolonged hospital stay
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who were 18 years of age or older and were scheduled to have a unilateral primary or revision total hip arthroplasty were eligible for the study.
Exclusion criteria	Serum creatinine level of at least 1.7mg per deciliter (150 micromoles per litre); defective hemostasis; documented gastrointestinal or other bleeding within 3 months before the operation; a cerebral haemorrhage within 3 months before the operation; an operative procedure involving the eye, ear or central nervous system within one month before the operation; a known hypersensitivity to heparin; severe hypertension; and a weight of less than 41kg; women who were pregnant or breast feeding and those with reproductive potential unless they had a negative pregnancy test

Study	Francis 1997[106]
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Dalteparin: 63 (13); Warfarin: 63 (14). Gender (M:F): Dalteparin: 127/144; Warfarin: 132/147. Ethnicity: % white - Dalteparin: 88; Warfarin: 94
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=271) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 5000 IU daily (standard dose) subcutaneously for mean of 7 days from the first postoperative day. First dose of 2500 IU was administered two hours before the operation; second dose of 2500 IU was given on the evening of the operation. Duration 9 days. Concurrent medication/care: No other investigational drugs were used concomitantly (n=279) Intervention 2: Vitamin K antagonists - Warfarin (all doses). Warfarin adjusted to an INR of approximately 2.5, orally. First dose administered the evening before the operation and second dose administered on the day of the operation. Dose: 5-75mg (depending on weight: 5mg for patients that weighed ≤57kg; 7.5 for patients that weighed >57kg). Duration 9 days. Concurrent medication/care: No other investigational drugs were used concomitantly
Funding	-- (Grant from the National Heart, Lung and Blood Institute; National Institute of Health, Bethesda, Maryland and a grant from Pharmacia-Upjohn, Kalamazoo, Michigan.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus WARFARIN (ALL DOSES)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 9 days; Group 1: 49/190, Group 2: 28/192
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 79; Group 2 Number missing: 89

Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 9 days; Group 1: 6/271, Group 2: 4/279
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Study	Francis 1997[106]
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Wound haematoma at 9 days; Group 1: 7/271, Group 2: 2/279 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT distal at 9 days; Group 1: 33/190, Group 2: 18/192 Protocol outcome 5: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at 9 days; Group 1: 16/190, Group 2: 10/192	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fuji 2008 [111] Country of study:	Patient group: Study 1: Total knee replacement (TKR) Study 2: Total hip replacement (THR)	Study 1 (TKR) Group 1 Fondaparinux (Atrixa) Start time: 24hr ±	All cause mortality	Study 1 (TKR) Group1: 0/84 Group 2: 0/87 P value: N/A Study 2 (THR) Group3: 0/81 Group 4: 0/82 P value: N/A	Funding: GlaxoSmithKlein, Sanovi-synthelabo and NV Organon

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Japan Study design: RCT List who was masked to interventions: Paper states that study is double blind and that the endpoint assessors were blinded. Evidence level: 1+ Duration of	Setting: Department of Orthopaedic Surgery Inclusion criteria: Patients of either gender if their age was 20 years or greater, and they were scheduled for TKR or THR surgery or revision surgery for TKR or THR Exclusion criteria: Active, clinically significant bleeding Bleeding tendency/disorder (e.g. ulcer of the digestive tract etc.) Severe hepatic disorder Hypersensitivity to UFH or LMWH Requirement of an indwelling intrathecal or epidural catheter during the treatment period [redacted] Brain, spine or ophthalmologic	2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous injections Group 2 Placebo (0.25ml isotonic sodium chloride) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous injections Additional non-	Fatal bleeding	Study 1 (TKR) Group1: 0/84 Group 2: 0/87 P value: N/A Study 2 (THR) Group3: 0/81 Group 4: 0/82 P value: N/A	Limitations: Method of randomisation not given. No details provided on allocation concealment. Outcomes not reported: DVT, PE, Heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
follow-up: 11-17 days	surgery within 3 months preceding enrolment Body weight <40kg Severe renal disorder (serum creatinine concentration >2.0mg/dL) Study 1 (TKR) All patients N: 426 No. of dropouts: 29 (6.8%) Age (mean): 71.0 (sd = 8.0) M/F: 75: 351 Additional risk factors: BMI ≥ 30 kg/m2 = 64 (15.0%) Group 1 No. randomised: 84 Group 2 No. randomised: 87 Study 2 (THR) All patients N: 406 No. of dropouts: 25 (6.2%) Age (mean): 61.6 (sd = 10.9) M/F: 73: 333 Additional risk factors: BMI ≥ 30 kg/m2 = 26 (6.4%) Group 3 No. randomised: 81	comparative prophylaxis: More than 50% of patients received elastic stockings /bandages for part of the study. Study 2 (THR) Group 3 Fondaparinux (Atrixa) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous injections Group 4 Placebo (0.25ml isotonic sodium chloride) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous	Major bleeding (description: fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with a bleeding index of 2 or more.)	Study 1 (TKR) Group1: 1/84 Group 2: 1/87 P value: 1.00* Study 2 (THR) Group3: 2/81 Group 4: 0/82 P value: 0.245*	Additional outcomes reported: Incidence of combined VTE was recorded Study 1 (TKR) Group 1: 16.2% Group 2: 65.3% P value: <0.05* Study 2 (THR) Group 3: 7.4% Group 4: 33.8% P value: <0.05* Notes: * calculated by NCC using fishers exact test. Study was a dose ranging study with separate groups receiving 0.75, 1.5, 2.5 and 3.0mg fondaparinux. Only the group receiving 2.5 mg fondaparinux is analysed here as this is the licensed dose.
			Minor bleeding (description: not defined)	Study 1 (TKR) Group1: 2/84 Group 2: 3/87 P value: 1.00* Study 2 (THR) Group3: 4/81 Group 4: 0/82 P value: 0.059*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 4 No. randomised: 82	injections Additional non-comparative prophylaxis: More than 50% of patients received elastic stockings /bandages for part of the study.			

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fuji 2008A [112] Country of study: Japan Study design: RCT List who was masked to interventions: Paper states that study is double blind (see limitations) and that the	Patient group: Study 1: Total knee replacement (TKR) Study 2: Total hip replacement (THR) Setting: Department of Orthopaedic Surgery Inclusion criteria: Patients aged ≥ 20 years (no upper age limit was applied) undergoing elective primary THR or TKR. Exclusion criteria: [redacted] Patients requiring revision TKR or revision THR	Study 1 (TKR) Group 1 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 20mg subcutaneous injection Group 2 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days	Symptomatic pulmonary Embolism (description: ventilation perfusion lung scans or pulmonary angiography at 90 days)	Study 1 (TKR) Group 1: 1/78 Group 2: 1/74 Group 3: 0/84 Group 4: 1/79 p value: Not significant Study 2 (THR) Group 5: 0/81 Group 6: 1/80 Group 7: 0/90 Group 8: 0/86 p value: Not significant	Funding: Sanofi-Aventis Limitations: Method of randomisation not given. No details provided on allocation concealment. Study reports that it was blinded but no information provided and some of the injection regimens were once daily whilst others were twice daily.
			DVT, asymptomatic or symptomatic (screened for by: Doppler ultrasound at 14 days)	Study 1 (TKR) Group 1: 34/78 Group 2: 26/74 Group 3: 25/84	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
endpoint assessors were blinded. Evidence level: 1+ Duration of follow-up: 90 days	Contraindication to heparin therapy Positive clinical evidence of chronic (post-phlebitic syndrome) or acute DVT within 12 months of the study drug treatment ■ Documented allergy to iodine or contrast medium ■ impaired renal function (creatinine clearance <30ml/min or plasma creatinine level >1.5mg/dl) Severe hepatic disease Uncontrolled hypertension Illicit drug use or alcohol abuse Treatment with other investigational agents within 3 months of surgery ■ Failure to achieve postoperative haemostasis ■ Female subjects if pregnant or breast- feeding. Study 1 (TKR) All patients N: 396 No. of dropouts: 32 (8.1%) Group 1 No. analysed: 78	Daily 40 mg subcutaneous injection Group 3 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Twice daily 20mg subcutaneous injections Group 4 Placebo (saline) Start time: 24-36 hrs after surgery Duration: 14 days Subcutaneous injections (no frequency stated) Additional non-comparative prophylaxis: More than 50% of patients received elastic stockings		Group 4: 48/79 p value: All groups receiving LMWH (gp 1,2 & 3) had significantly less DVT than the placebo group (gp 4). Group 1 vs. Group 4 = 0.038* Group 2 vs. Group 4 = 0.002* Group 3 vs. Group 4 = <0.001* No other significant differences between groups were found. Study 2 (THR) Group 5: 21/81 Group 6: 27/80 Group 7: 18/90 Group 8: 36/86 p value: The group receiving twice daily injections of 20mg LMWH (gp 7) had significantly less DVT than the placebo group (gp 8) p = 0.003* No other significant differences between groups were found	Outcomes not reported: All cause mortality, fatal bleeding, fatal PE, heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay Additional outcomes reported: The total number of adverse events were recorded. The authors concluded that most of these were not related to the treatment under investigation. Notes: * calculated by NCC using fishers exact test.
			Thigh DVT	Study 1 (TKR)	
			(description: screened for by:	Group 1: 6/78	
			Doppler ultrasound at 14	Group 2: 3/74	
			days)	Group 3: 0/84	
				Group 4: 6/79	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		/bandages for part of the study. No other prophylaxis was used.			
	Age (mean): 68.8 (sd = 9.0) M/F: 15:63 Additional risk factors: BMI ≥ 25 kg/m2 = 40 (51.3%) Group 2 No. analysed: 74 Age (mean): 70.0 (sd = 9.4) M/F: 11:63 Additional risk factors: BMI ≥ 25 kg/m2 = 44 (59.4%) Group 3 No. analysed: 84 Age (mean): 68.3 (sd = 8.7) M/F: 5:79 Additional risk factors: BMI ≥ 25 kg/m2 = 35 (41.7%) Group 4 No. analysed: 79 Age (mean): 68.7 (sd =9.5) M/F: 15: 64 Additional risk factors: BMI ≥ 25 kg/m2 = 40 (50.6%)	Study 2 (THR) Group 5 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 20mg subcutaneous injections Group 6 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 40 mg subcutaneous injections Group 7 LMWH (Enoxaparin) Start		p value: There were significantly fewer events in the twice daily 20mg LMWH group (gp3) vs the once daily 20mg LMWH group (gp 1) (p = 0.011*). There were significantly fewer events in the twice daily 20mg LMWh group (gp3) vs. the placebo group (gp 4) (p = 0.012*) Study 2 (THR) Group 5: 3/81 Group 6: 6/80 Group 7: 3/90 Group 8: 9/86 p value: No significant difference	
			Major bleeding (description: bleeding episode that was retroperitoneal, intracranial, or intraocular o if it was associated with: death; transfusion of ≥2 units of packed red blood cells or whole blood (except autologous); a reduction of	Study 1 (TKR) Group 1: 0/89 Group 2: 1/91 Group 3: 3/95 Group 4: 4/89 p value: Not significant Study 2 (THR) Group 5: 1/100 Group 6: 2/102 Group 7: 3/104	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Study 2 (THR) All patients N: 436 No. of dropouts: 29 (6.7%) Group 5 No. analysed: 81 Age (mean): 63.3 (sd = 10.4) M/F: 10: 71 Additional risk factors: BMI ≥ 25 kg/m2 = 23 (28.4%) Group 6 No. analysed: 80 Age (mean): 60.6 (sd = 9.9) M/F: 6:74 Additional risk factors: BMI ≥ 25 kg/m2 = 26 (35.2%) Group 7 No. analysed: 90 Age (mean): 63.0 (sd = 9.3) M/F: 15:75 Additional risk factors: BMI ≥ 25 kg/m2 = 31 (34.4%) Group 8 No. analysed: 86 Age (mean): 62.0 (sd =10.3) M/F: 11: 75	time: 24-36 hrs after surgery Duration: 14 days Twice daily 20mg subcutaneous injections Group 8 Placebo (saline) Start time: 24-36 hrs after surgery Duration: 14 days Subcutaneous injections (no frequency stated) Additional non-comparative prophylaxis: More than 50% of patients received elastic stockings /bandages for part of the study. No other prophylaxis was used.	≥2 g/d; or a serious or life threatening clinical events that required medical intervention.)	Group 8: 0/101 p value: Not significant	
		Minor bleeding (description: at least one of the following features: epistaxis lasting >5 minutes or requiring intervention; ecchymosis or hematoma with a maximum size of >5 cm; haematuria not associated with urinary catheter trauma; gastrointestinal haemorrhage not related to intubation or a nasogastric tube; wound haematoma or haemorrhagic wound complications not associated with major haemorrhage; or subconjunctival haemorrhage requiring cessation of medication)	Study 1 (TKR) Group 1: 5/89 Group 2: 6/91 Group 3: 10/95 Group 4: 4/89 p value: Not significant Study 2 (THR) Group 5: 1/100 Group 6: 7/102 Group 7: 4/104 Group 8: 2/101 p value: Not significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Additional risk factors: BMI ≥ 25 kg/m2 = 34 (39.5%)				

Study	Gallus 1983[114]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Australia; Setting: Medical Centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged over 50 years admitted to Flinders Medical Centre for elective hip replacement
Exclusion criteria	Refusal to participate, operated leg placed in balanced traction after surgery, refused venography, failed venography
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): IPCD group 69 (16); control group 67 (16). Gender (M:F): 1:2. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Intermittent pneumatic compression devices - Full leg. A B.O.C.-Roberts Venous Flow Stimulator was used for intermittent calf compression, 45 mmHg for 10 seconds each 2 minutes. Device was applied to both legs throughout surgery then day and night for 7 days. It was temporarily removed to permit physiotherapy, ambulation and skin care. Duration 7 days. Concurrent medication/care: n/a (n=47) Intervention 2: No treatment - Usual care. No further details reported. Duration 7 days. Concurrent medication/care: n/a
Funding	Funding not stated

Study	Gallus 1983[114]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IPCD versus CONTROL GROUP Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 7 days; Group 1: 15/43, Group 2: 25/47 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Hampson 1974[136]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in United Kingdom; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 18 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by 125I fibrinogen uptake test and ultrasound investigations
Stratum	Overall

Study	Hampson 1974[136]
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged between the ages of 60-80 years undergoing hip replacement arthroplasty
Exclusion criteria	People having undergone previous hip surgery, a history of malignant disease, diabetes, rheumatoid arthritis, or previous thromboembolism.
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): UFH: 68 (5.9); Control: 68.2 (5.0). Gender (M:F): UFH: 17/31; Control: 18/34. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Calcium heparin, 5000 IU subcutaneously three times daily for 7-10 days after surgery. Duration 18 days. Concurrent medication/care: Not reported (n=52) Intervention 2: No treatment - Placebo. Saline subcutaneously three times daily. Duration Not reported. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 18 days; Group 1: 22/48, Group 2: 28/52
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 18 days; Group 1: 0/48, Group 2: 0/52
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Study	Hampson 1974[136]
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study (subsidiary papers)	Hardwick 2011[137] (Colwell 2010[70])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=395)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 10 days + Follow-up 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The intent to detect DVT by bilateral duplex ultrasound was described in the methods section but the intended method for detecting/diagnosing PE was not described in the methods section but was later reported in the results section (spiral computed tomographic scans were used for PE).
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Older than 18 and scheduled for a unilateral total hip arthroplasty
Exclusion criteria	History of thrombosis; mental deficiency; known coagulation disorder; solid malignant tumour; peptic ulcer disease
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): MCD 63 vs. Enoxaparin 64 (20-88 for both groups). Gender (M:F): 178:214. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Extra comments	.
Indirectness of population	No indirectness: Ethnicity was not reported
Interventions	(n=198) Intervention 1: Intermittent pneumatic compression devices - Below knee. Mobile compression device (ActiveCare+SFT, Medical Compression Systems, Or Akiva, Israel) with its Velcro sleeves fastened around the calf was applied in the operating room and continued use for 10 days after surgery. Duration 10 days. Concurrent medication/care: Participants in this group could receive aspirin 81mg daily at the discretion of the surgeon. (n=194) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous injection 30mg every 12 hrs starting the morning after surgery while in the hospital then 40mg once daily after hospital discharge for 10 days. Duration Average of 3 days hospital stay + 10 days post-discharge. Concurrent medication/care: Aspirin was used in addition to the compression device in 63% of patients in this group.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MOBILE COMPRESSION DEVICE versus ENOXAPARIN

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: Incidence of DVT at 10 to 12 days after surgery (or 3 months - unclear); Group 1: 8/196, Group 2: 8/190; Comments: N.B. Four patients in the MCD group took aspirin 81mg daily.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - The authors reported that 63% of the participants in the MCD group used aspirin (assumed to be on a daily basis) and this affects comparability of care. It is stated that 395 patients were randomised, however, the numbers displayed in each group are 198 for the MCD group and 194 for the enoxaparin group (392 in total). It is unknown as to what happened to the 3 participants unaccounted for. In addition, 6 people are missing from the efficacy analyses which was said to have applied "intent-to-treat method", however, it is unclear why data for 6 people are not provided. Furthermore, the method of detecting and confirming VTE events were not described fully in the method section. ; Indirectness of outcome: No indirectness, Comments: It is unclear whether the incidences of VTE events presented in the article occurred over 10 to 12 days (treatment period) or 3 months (follow-up period).; Baseline details: Except for diagnosis of osteoarthritis there is no baseline data about the health status or co-morbidities of the participants; Group 1 Number missing: 2, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Incidence of PE at 10 to 12 days after surgery (or 3 months - unclear); Group 1: 2/196, Group 2: 2/194; Comments: N.B. One patient in the MCD group received aspirin 81mg daily.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - The authors reported that 63% of the participants in the MCD group used aspirin (assumed to be on a daily basis) and this affects comparability of care. It is stated that 395 patients were randomised, however, the numbers displayed in each group are 198 for the MCD group and 194 for the enoxaparin group (392 in total). It is unknown as to what happened to the 3 participants unaccounted for. In addition, 6 people are missing from the efficacy analyses which was said to have applied "intent-to-treat method", however, it is unclear why data for 6 people are not provided. Furthermore, the method of detecting and confirming VTE events were not described fully in the method section. ; Indirectness of outcome: No indirectness, Comments: It is unclear whether the incidences of VTE events presented in the article occurred over 10 to 12 days (treatment period) or 3 months (follow-up period).; Baseline details: Except for diagnosis of osteoarthritis there is no baseline data about the health status or co-morbidities of the participants; Group 1 Number missing: 2, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 10 to 12 days after surgery; Group 1: 0/198, Group 2: 11/194; Comments: p=0.0004
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - The authors reported that 63% of the participants in the MCD group used aspirin (assumed to be on a daily basis) and this affects comparability of care. It is stated that 395 patients were randomised, however, the numbers displayed in each group are 198 for the MCD group and 194 for the enoxaparin group (392 in

total). It is unknown as to what happened to the 3 participants unaccounted for. Furthermore, "major bleeding" has not been defined.; Indirectness of outcome: No indirectness, Comments: Definition of major bleeding not provided; Baseline details: Except for diagnosis of osteoarthritis there is no baseline data about the health status or co-morbidities of the participants; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: VTE at 7-90 days from hospital discharge - Actual outcome: Incidence of VTE at 10 to 12 days after surgery (or 3 months - unclear); Group 1: 10/196, Group 2: 10/190	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Hull 1990[152]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=310)
Countries and setting	Conducted in Canada; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing total hip replacement who had no history of VTE
Exclusion criteria	Allergic to venographic dye, unable to wear the compression cuffs, required treatment with aspirin, refused informed consent
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): IPCD group 64 (11); control group 66 (12). Gender (M:F): 1:1.5. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=152) Intervention 1: Intermittent pneumatic compression devices - Mixed full leg/below knee. Sequential calf and thigh intermittent compression begun postoperatively in the recovery room. Each calf cuff contained four chambers, and each thigh cuff contained two chambers. Intermittent compression was achieved using an electric pump that inflated the six chambers sequentially at 5-second intervals to a pressure of 50-65 mmHg, beginning with the most distal calf chamber and progressing proximally. Pressure in all six chambers was maintained for an additional 5 seconds, for a total inflation time of 35 seconds; the six chambers were then delfated simultaneously for 25 seconds. Duration Until hospital discharge or at 14 days. Concurrent medication/care: Routine physiotherapy was given to all patients in both study groups. (n=158) Intervention 2: No treatment - Usual care. Control group - no further details reported. Duration Until hospital discharge or at 14 days. Concurrent medication/care: Routine physiotherapy was given to all patients in both study groups.
Funding	Academic or government funding (Supported by grants from the Ontario Ministry of Health, Toronto, Canada; the Heart and Stroke Foundation of Ontario, Toronto, Canada; and the Canadian Heart Foundation, Ottawa)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IPCD versus CONTROL GROUP Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 14 days; Group 1: 36/152, Group 2: 77/158 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 14 days; Group 1: 1/152, Group 2: 1/158 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Hull 2000[151]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1472)
Countries and setting	Conducted in Canada, USA; Setting: Multicentre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years and scheduled for elective unilateral total hip arthroplasty with informed consent
Exclusion criteria	Documented bleeding within 3 months before surgery; known hypersensitivity to heparin, LMWH, warfarin, or contrast media; defective hemostasis (e.g. thrombocytopenia); ongoing anticoagulants; pregnancy or breast feeding; clinically significant hepatic dysfunction; renal insufficiency (serum creatinine level >150µmol/L [1.7mg/dL]); severe hypertension (diastolic blood pressure >120mmHg); septic endocarditis; weight of less than 40kg; eye, ear or central nervous system surgery within 1 month before surgery; diseases with unfavourable prognosis (e.g. malignant neoplasms or other intercurrent disease making study participation impractical or medically complicated); inability to follow instructions or perform procedures, including self-injections required during the home prophylaxis study; simultaneous participation in another pharmacological study or use of any investigational drug within 30 days before surgery; previous randomisation into this study; or use of pneumatic compression stockings
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Preop LMWH 64 (12); postop LMWH 63 (13); wafarin 63 (13). Gender (M:F): 1:1.08. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean (SD) BMI: preop LMWH 29 (6), postop LMWH 29 (6), warfarin 28 (5)). 2. Renal impairment: Not applicable
Indirectness of population	--
Interventions	(n=496) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Preoperative Dalteparin - initial dose of 2500IU within 2 hours before surgery, patients then received a second dose of dalteparin (2500IU) at least 4 hours postoperatively, subcutaneously. On subsequent days, all patients receiving dalteparin were given 5000IU subcutaneously once daily each morning. Also, received placebo oral capsules. Duration 4-8 days or until discharge (duration unclear). Concurrent medication/care: n/a

	(n=487) Intervention 2: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Post-operative dalteparin - initial placebo dose within 2 hours before surgery, patients then received first active dose of dalteparin (2500IU) at least 4 hours postoperatively, subcutaneously. On subsequent days, all patients receiving dalteparin were given 5000IU subcutaneously once daily each morning. Also, received placebo oral capsules. Duration 4-8 days or until discharge (duration unclear). Concurrent medication/care: n/a (n=489) Intervention 3: Vitamin K antagonists - Warfarin (all doses). Patients received an initial dose postoperatively on the evening of surgery day. The initial dose was 10mg, except for patients aged 70 years or older or weighing less than 57kg who received a 5mg dose. Thereafter, warfarin doses were adjusted daily to maintain an INR from 2.0 to 3.0. Patients also received subcutaneous placebo injections. Duration 4-8 days or until discharge (duration unclear). Concurrent medication/care: n/a
Funding	Study funded by industry (Support for this trial was provided through a grant-in-aid by Pharmacia & Upjohn to the University of Calgary)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRE-OPERATION DALTEPARIN versus POST-OPERATION DALTEPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 8 days; Group 1: 2/496, Group 2: 0/487
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 8 days; Group 1: 36/337, Group 2: 44/336
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 159, Reason: Did not receive study medication - cancelled operation, presence of exclusion criteria, withdrawn consent, miscellaneous reasons making the patient ineligible.; Group 2 Number missing: 151, Reason: Did not receive study medication - cancelled operation, presence of exclusion criteria, withdrawn consent, miscellaneous reasons making the patient ineligible.

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 8 days; Group 1: 0/496, Group 2: 0/487
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 8 days; Group 1: 44/496, Group 2: 32/487
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Surgical site haematoma at up to 45 days from hospital discharge
- Actual outcome: Wound haematoma at 8 days; Group 1: 2/496, Group 2: 2/487
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRE-OPERATION DALTEPARIN versus WARFARIN (ALL DOSES)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 8 days; Group 1: 2/496, Group 2: 2/489
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 8 days; Group 1: 36/337, Group 2: 81/338
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 159, Reason: Did not receive study medication - cancelled operation, presence of exclusion criteria, withdrawn consent, miscellaneous reasons making the patient ineligible.; Group 2 Number missing: 151, Reason: Did not receive study medication - cancelled operation, presence of exclusion criteria, withdrawn consent, miscellaneous reasons making the patient ineligible.

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 8 days; Group 1: 0/496, Group 2: 0/489
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening

clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 8 days; Group 1: 44/496, Group 2: 22/489
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Surgical site haematoma at up to 45 days from hospital discharge
- Actual outcome: Wound haematoma at 8 days; Group 1: 2/496, Group 2: 1/489
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POST-OPERATION DALTEPARIN versus WARFARIN (ALL DOSES)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 8 days; Group 1: 0/487, Group 2: 2/489
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 8 days; Group 1: 44/336, Group 2: 81/338
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 159, Reason: Did not receive study medication - cancelled operation, presence of exclusion criteria, withdrawn consent, miscellaneous reasons making the patient ineligible.; Group 2 Number missing: 151, Reason: Did not receive study medication - cancelled operation, presence of exclusion criteria, withdrawn consent, miscellaneous reasons making the patient ineligible.

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 8 days; Group 1: 0/487, Group 2: 0/489
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 8 days; Group 1: 32/487, Group 2: 22/489
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Wound haematoma at 8 days; Group 1: 2/487, Group 2: 1/489 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Kakkar 2000 [167]	RCT	1+	Total: 298 Intervention n: 149 Control n: 149	Type of surgery: Patients scheduled for elective hip replacement surgery. Duration of surgery: Int: 110±55.1 Control: 100±58.7; p=0.207 Age and gender: Intervention: Mean age: 70.4 ± 10.9 years M/F:49/100 Control: Mean age: 70.5 ± 9.2 years M/F:45/104 Pre-existing risk factors: Previous DVT: Int:	Type, dose and timing: One dose daily of subcutaneous LMWH (3500 IU of Bemiparin) plus a placebo injections of 0.9% saline. Prophylaxis started 2 hours before surgery and continued for at least 8 post-operative days or longer if patient was still institutionalised. Additional non-comparative prophylaxis: Some patients	Type, dose and timing: 5000 units of Calcium heparin injected subcutaneously twice daily. Prophylaxis started 2 hours before surgery and continued for at least 8 post-operative days or longer if patient was still institutionalised. Additional non-comparative	4 weeks	VTE total	Int: 9/125 (7.2%) Cont: 25/134 (18.7%) p=0.01	Financially supported by Laboratories Farmaceuticos Rovi S.A.; (Madrid, Spain) Who also provided supply of LMWH and std UFH sodium Also reported: Operative blood loss, postoperative drain loss
								DVT confirmed by bilateral elective venography.	Int: 9/101 (8.9%) Cont: 24/116 (20.7%) p=0.03	
								Proximal DVT:	Int: 3/101 (3.0%) Cont: 5/116 (4.3%) p=0.73	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				n = 4 Control: n = 12; Previous PE: Int: n = 1 Control: n = 3; Varicose veins: Int: n = 44 Control: n = 46; Varicose ulcer: Int: n = 3 Control: n = 6; obesity: Int: n = 23 Control: n = 27;	had analgesics including aspirin (LMWH 56.4% and UFH 59.1%)	prophylaxis: Some patients had analgesics including aspirin (LMWH 56.4% and UFH 59.1%)		Distal DVT:	Int: 4/101 (4.0%) Cont: 13/116 (11.2%) p=0.08	
								Proximal and Distal DVT:	Int: 2/101 (2.0%) Cont: 6/116 (5.2%) p=0.23	
								PE Confirmed by ventilation perfusion scan.	Int: 1/125 (0.8%) Cont: 2/134 (1.5%) p=1.00	
								Patient transfused	Int: n = 74/149 Control: n = 66/149; p=0.42	
								Wound hematomas	Int: n = 8/149 Control: n = 7/149; p=1.00	

Study	Kakkar 2008[162]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2509)
Countries and setting	Conducted in Multiple countries, Unknown multicentre; Setting: 123 centres across 21 countries worldwide

Study	Kakkar 2008[162]
Line of therapy	Not applicable
Duration of study	Intervention time: Rivaroxaban (31-39 days); LMWH (10-14 days)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by venography PE: confirmed by pulmonary angiography, perfusion/ventilation lung scintigraphy with chest radiography, or spiral computed tomography. Major bleeding: defined as bleeding that was fatal, was into a critical organ (retroperitoneal, intracranial, intraocular, intraspinal), required re-operation, or clinically overt extra surgical site bleeding associated with a fall in haemoglobin of 20 g/L or more, calculated from the day 1post-operative baseline value, or requiring infusion of two or more units of whole blood or packed cells.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18 years or over, who were scheduled to undergo elective total hip arthroplasty.
Exclusion criteria	Patients scheduled to undergo staged bilateral hip arthroplasty, had active bleeding or a high risk of bleeding, or had any condition contraindicating the use of enoxaparin or that might require enoxaparin dose adjustment, including severe renal impairment. Other exclusions: significant liver disease, pregnancy or breastfeeding, concomitant use of HIV protease inhibitors, use of fibrinolytic therapy or planned intermittent pneumatic compression during the study period, conditions preventing bilateral venography.
Recruitment/selection of patients	Patients were enrolled between February 2006 and April 2007.
Age, gender and ethnicity	Age - Mean (SD): 61.6 years. Gender (M:F): 1/1. Ethnicity: White 65%, Asian 20%, Hispanic 12%, Black 3%
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean: 27 kg/m2). 2. Renal impairment: Not applicable
Extra comments	History of VTE: rivaroxaban 0.8%; enoxaparin 1.6%.
Indirectness of population	No indirectness
Interventions	(n=1252) Intervention 1: Rivaroxaban - Rivaroxaban (all doses). Patients were given 10mg rivaroxaban once daily, orally (Xarelto, Bayer HealthCare). Course of rivaroxaban was started 6-8 hours after wound closure and continued for 31-39 days, patients also received placebo injections for 10-14 days starting 12 hours before surgery. Duration 31-39 days. Concurrent medication/care: n/a (n=1257) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Patients were given subcutaneous injections of enoxaparin 40mg (Clexane/Lovenox, Sanofi-Aventis) once daily. Enoxaparin was initiated 12 hours before surgery and restarted 6-8 hours after wound closure and continued for 10-14 days, patients also received placebo tablets for 31-39 days starting 6-8 hours after wound closure. Duration 31-39

Study	Kakkar 2008[162]
	days. Concurrent medication/care: n/a
Funding	Study funded by industry (Bayer HealthCare AG, Johnson & Johnson Pharmaceutical Research and Development LLC)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN (EXTENDED DURATION) versus ENOXAPARIN (STANDARD DURATION)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 30-42 days; Group 1: 17/864, Group 2: 81/869
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 338, Reason: Details not reported; Group 2 Number missing: 388, Reason: Details not reported

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 30-42 days; Group 1: 14/864, Group 2: 71/869
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 338, Reason: Details not reported; Group 2 Number missing: 388, Reason: Details not reported

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 30-42 days; Group 1: 1/864, Group 2: 4/869
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 338, Reason: Details not reported; Group 2 Number missing: 388, Reason: Details not reported

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 30-42 days; Group 1: 1/1228, Group 2: 1/1229
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 24, Reason: Details not reported; Group 2 Number missing: 28, Reason: Details not reported

Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge
- Actual outcome: Clinically relevant non-major bleeding at 30-42 days; Group 1: 40/1228, Group 2: 33/1229
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;

Study	Kakkar 2008[162]
Indirectness of outcome: No indirectness ; Group 1 Number missing: 24, Reason: Details not reported; Group 2 Number missing: 28, Reason: Details not reported Protocol outcome 6: Infection at duration of study - Actual outcome: Wound infection at 30-42 days; Group 1: 8/1228, Group 2: 6/1229 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24, Reason: Details not reported; Group 2 Number missing: 28, Reason: Details not reported Protocol outcome 7: VTE at 7-90 days from hospital discharge - Actual outcome: Major VTE at 30-42 days; Group 1: 6/961, Group 2: 49/962 - Actual outcome: Symptomatic VTE at 30-42 days; Group 1: 3/1212, Group 2: 15/1207 Protocol outcome 8: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 30-42 days; Group 1: 27/869, Group 2: 9/864 Protocol outcome 9: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 30-42 days; Group 1: 5/864, Group 2: 44/869 Protocol outcome 10: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at 30-42 days; Group 1: 0/1228, Group 2: 0/1229	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Kalodiki 1996[169]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8-12 days

Study	Kalodiki 1996[169]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by bilateral ascending venography. PE confirmed by perfusion/ventilation scan.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People older than 40 years who were having unilateral total hip replacement for the first time or without cement under general anaesthesia.
Exclusion criteria	Established documented bleeding disorders, abnormal preoperative coagulation tests (prothrombin time and activated partial thromboplastin time) including platelet counts below 100x10^9/l acute bleeding and/or recently documented haemorrhage and any other bleeding risk were excluded. Other exclusion criteria included anticoagulant therapy during the 14 days before surgery or during the study, aspirin or non-steroidal anti-inflammatory drugs 5 and 2 days before surgery respectively, severe arterial hypertension, history of stroke during the previous six months and/or neurosurgery, endocarditis, acute or chronic renal failure, severe hepatic and/or pancreatic disease, hypersensitivity to heparin or metabisulphite, allergy to porcine derived products, iodine or radiopaque contrast media, history of heparin induced thrombocytopenia, previous surgery of the ipsilateral hip, surgery carried out under regional anaesthesia, clinical signs of DVT and/or history of recent DVT and/or PE, presence of malignant growths, mental disorders and/or failure to give informed consent.
Recruitment/selection of patients	Consecutive recruitment
Age, gender and ethnicity	Age - Other: Mean age: LMWH: 67; LMWH&AES: 69; Placebo: 72. Gender (M:F): LMWH: 13/18; LMWH&AES: 19/13; Placebo: 6/8. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: No treatment - Placebo. Placebo (normal saline) once daily subcutaneously. Duration 8-12 days. Concurrent medication/care: Not reported (n=32) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin dose 40 mg (4000 Anti Xa iU) administered subcutaneously 12 hours before operation and then once daily until discharge. Duration 8-12 days. Concurrent medication/care: Not reported (n=32) Intervention 3: Anti-embolism stockings - Above knee. LMWH+ AES: Enoxaparin dose 40 mg (4000 Anti Xa iU) administered subcutaneously 12 hours before operation and then once daily until discharge + thigh-high TED stockings applied before operation on both legs and not taken off until patient discharged. Duration 8-12 days. Concurrent medication/care: Not reported

Study	Kalodiki 1996[169]
	(n=14) Intervention 4: No treatment - Placebo. Identically labelled placebo injections (normal saline) administered subcutaneously 12 hours before operation and then once daily until discharge. Duration 8-12 days. Concurrent medication/care: Not reported
Funding	Study funded by industry (Rhone-Poulenc-Rorer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT confirmed by venograms at 8-12 days; Group 1: 12/32, Group 2: 13/14
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Patients assigned to LMWH +AES were not blinded to the AES portion of the intervention; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE confirmed by high probability perfusion/ventilation lung scan at 8-12 days; Group 1: 3/29, Group 2: 5/12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Patients assigned to LMWH +AES were not blinded to the AES portion of the intervention; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: DVT (distal) at 7-90 days from hospital discharge
- Actual outcome: DVT (distal) confirmed by venograms at 8-12 days; Group 1: 3/32, Group 2: 5/14

Protocol outcome 4: DVT (proximal) at 7-90 days from hospital discharge
- Actual outcome: DVT (proximal) confirmed by venograms at 8-12 days; Group 1: 9/32, Group 2: 8/14

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus ABOVE KNEE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler)

Study	Kalodiki 1996[169]
ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT confirmed by venograms at 8-12 days; Group 1: 12/32, Group 2: 8/32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Patients assigned to LMWH +AES were not blinded to the AES portion of the intervention; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE confirmed by high probability perfusion/ventilation lung scan at 8-12 days; Group 1: 3/29, Group 2: 2/31 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Patients assigned to LMWH +AES were not blinded to the AES portion of the intervention; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) confirmed by venograms at 8-12 days; Group 1: 3/32, Group 2: 4/32 Protocol outcome 4: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) confirmed by venograms at 8-12 days; Group 1: 9/32, Group 2: 4/32 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABOVE KNEE versus PLACEBO Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT confirmed by venograms at 8-12 days; Group 1: 8/32, Group 2: 13/14 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Patients assigned to LMWH +AES were not blinded to the AES portion of the intervention; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE confirmed by high probability perfusion/ventilation lung scan at 8-12 days; Group 1: 2/31, Group 2: 5/12 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Patients assigned to LMWH +AES were not blinded to the AES portion of the intervention; Group 1 Number

Study	Kalodiki 1996[169]
missing: ; Group 2 Number missing: Protocol outcome 3: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) confirmed by venograms at 8-12 days; Group 1: 4/32, Group 2: 5/14 Protocol outcome 4: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) confirmed by venograms at 8-12 days; Group 1: 4/32, Group 2: 8/14	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Lassen 1991[191]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=190)
Countries and setting	Conducted in Denmark; Setting: Aalborg Hospital and Arhus Municipal Hospital, Denmark
Line of therapy	Not applicable
Duration of study	Intervention time: 8-10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 40 years or over scheduled for elective hip replacement

Study	Lassen 1991[191]
Exclusion criteria	Treatment with plasma expanders or investigational drugs within 4 weeks prior to the operation; impaired renal or hepatic function; uncontrolled hypertension (diastolic pressure >120mmHg); haemorrhagic diathesis; pregnancy; confinement to bed; revision arthroplasty; hypersensitivity to radiopaque dye, heparin, bisulfite, or benzyl alcohol; ongoing anticoagulant therapy; and lack of informed consent
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): UFH group 67 (40-85); placebo group 67 (40-86). Gender (M:F): 1:1. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=93) Intervention 1: Low molecular weight heparin (not licensed in UK) - Bemiparin (2500 units once daily - 3500 units once daily). 50 units anti-Xa per kg body given subcutaneously once daily. Injections were started 2 hours preoperatively and continued for 7 days. Also, received thigh-length AES, applied to both legs 1 hour before the operation and were day and night. During the operation the AES on the operated side was pulled down to below the knee level. Duration 7 days. Concurrent medication/care: N/A (n=97) Intervention 2: No treatment - Placebo. Placebo, saline subcutaneously once daily. Also, received thigh-length AES, applied to both legs 1 hour before the operation and were day and night. During the operation the AES on the operated side was pulled down to below the knee level. Duration 7 days. Concurrent medication/care: N/A
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEMIPARIN (2500 UNITS ONCE DAILY - 3500 UNITS ONCE DAILY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 8-10 days; Group 1: 29/93, Group 2: 44/97
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 8-10 days; Group 1: 1/93, Group 2: 1/97
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Study	Lassen 1991[191]
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	DaPP trial: Lassen 1998[190]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=Dalteparin (extended duration): 140; Dalteparin (standard duration): 141)
Countries and setting	Conducted in Denmark; Setting: 8 Danish orthopaedic centres (Aalborg, Silkeborg, Kolding, Horsens, Holstebro, Slagelse, Viborg, and Gentofte hospitals)
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 35 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The criterion for DVT was presence of intraluminal filling defects in at least two projections. The criteria for DVT used in the ultrasound examinations were presence of an intraluminal echo in the deep veins and/or loss of compressibility in a venous segment. The criteria for PE were those reported by PIOPED.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted for total hip arthroplasty (primary or revision) between January and November 1994.
Exclusion criteria	Aged under 18 years; previous surgery in the study; simultaneous participation in other pharmacological studies;

Study	DaPP trial: Lassen 1998[190]
	informed consent not obtained; high probability for drop-out; renal insufficiency (creatinine ≤200µmol/l); hepatic insufficiency and prothrombin <0.7 (relative activity); platelet count <100x10*9/L; treatment with oral anticoagulants or heparin within seven days before inclusion; hypersensitivity to heparin, LMWH or contrast media; documented bleeding within three months prior to surgery; intracranial bleeding within 3 months prior to surgery; eye, ear, or CNS surgery within one month prior to surgery; hypertension with diastolic pressure >120mmHg; septic endocarditis; body weight <40kg; and known pregnancy or lactation.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): Dalteparin: 68 (30-94); Placebo: 70 (28-91). Gender (M:F): Dalteparin: 66/74; Placebo: 62/79. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=140) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 5000 IU once daily (standard dose) subcutaneously from 12 hours before operation until 35 days after operation (extended duration). Duration 35 days. Concurrent medication/care: AES permitted (n=141) Intervention 2: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 5000 IU once daily (standard dose) subcutaneously from 12 hours before operation until 7 days after operation (standard duration). Placebo, isotonic sodium chloride subcutaneously administered until 35 days. Duration 35 days. Concurrent medication/care: AES permitted
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 35 days; Group 1: 5/113, Group 2: 12/102
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous DVT - Dalteparin (extended duration): 10; Dalteparin (standard duration): 5; Group 1 Number missing: 27; Group 2 Number missing: 39

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect;

Study	DaPP trial: Lassen 1998[190]
autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 35 days; Group 1: 0/140, Group 2: 0/141 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous DVT - Dalteparin (extended duration): 10; Dalteparin (standard duration): 5; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding (definition not reported) at 35 days; Group 1: 0/140, Group 2: 1/141 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous DVT - Dalteparin (extended duration): 10; Dalteparin (standard duration): 5; Group 1 Number missing: 27; Group 2 Number missing: 39 Protocol outcome 4: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT distal at 35 days; Group 1: 4/113, Group 2: 7/102 Protocol outcome 5: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at 35 days; Group 1: 1/113, Group 2: 5/102	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Lassen 2002[189]	RCT	1+	Total: 2309 Intervention n: 1155 Control n: 1154	Type of surgery: Patients scheduled for primary elective total hip-replacement surgery or revision of at	2.5 mg of Fondaparinux sodium and a placebo. The first active dose was given 6±2 hrs postoperatively	40 mg of Enoxaparin 1x/day and placebo. The first active dose was given 12±2 hrs preoperatively	49 days study period 11 days	DVT Confirmed by: systematic bilateral ascending venography (number of events/ total number)	Int: 36/908 Control: 83/918 p value: <0.0001; RRR:- 56.1% (95% CI)	Funding: study supported by NV Organon and Sanofi-Synthelabo. * ** defined as fatal

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			Dropouts (not treated): Int: 15 Comp: 21 Dropouts (not available for analysis): Int: 232 Comp: 214	least one component of a previously implanted total hip prosthesis. Duration of surgery: 2.4 hours, SD: ±0.83 Intervention: Mean age: 67, range: 30-90; M/F:396/512 Control: Mean age: 67, range: 24-97; M/F:402/517 Pre-existing risk factors: History of VTE: Intervention: 35 (4%) Control: 40 (4%).	and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. Additional non-comparative prophylaxis: The use of AES and physiotherapy was recommended No. patients receiving/using: AES = 649/908 Anticoagulant/antiplat elet therapy (not aspirin = 29/908 NSAIDs or aspirin: 483/908	and the second 12 to 24 hours postoperatively. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. Additional non-comparative prophylaxis: The use of AES and physiotherapy was recommended No. patients receiving/using: AES = 654/919 Anticoagulant/ant		VTE	Int: 37/908 Control: 85/919 p value: < 0.0001 RRR (95 % CI) -55.9 (-72.8 to -33.1)	bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								Symptomatic DVT	Int: 3/1129 Control: 1/1123 p value: 0.6247	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				Orthopaedic surgery within the previous 12 months: Intervention: 85 (9%) Control: 84 (9%)		iplatelet therapy (not aspirin) = 30/919 NSAIDs or aspirin: 493/919		Proximal DVT * Confirmed by: systematic bilateral ascending venography	Int: 6/922 Control: 23/927 p value: 0.002	
								Non-fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy Follow-up: 49 days	Int: 3/1129 Control: 3/1123 p value: N/A	
								Fatal PE Confirmed by: Follow-up: 49 days	Int: 1/1129 Control: 1/1123 p value: N/A	
								Major bleeding **	Int: 47/1140 Control: 32/1133 p value: 0.57	
								Fatal bleeding	Int: 0/1140 Control: 0/1133	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
									p value: N/A	
								Bleeding leading to re-operation	Int: 5/1140 Control: 3/1133 p value: 0.7261	
								other bleeding – number (%)	Int: 44/1140 Control: 38/1133 p value: 0.5743	
								Postoperative transfusions – number (%)	Int: 714/1140 Control: 690/1133 p value:	
								Death from any cause - number (%) Up to day 11	Int: 0/1140 Control: 2/1133 p value: 0.4122 Int: 2/1140 Control: 4/1133 p value: 0.4122	
								Death from any cause - number (%) Up to day 49		

Study	ADVANCE-3 trial: Lassen 2010[194]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=5407)
Countries and setting	Conducted in Multiple countries; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 32 to 38 days + Follow-up at 65 and 95 days after surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Mandatory bilateral venography was performed on the participants on certain days, presumably for DVT assessment, but no other specific diagnostic equipments have been mentioned in the method section, for example for assessment of PE. "Objective tests were performed in patients with clinically suspected VTE to confirm or rule out the diagnosis". Autopsy was performed whenever possible.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Anyone scheduled to undergo elective total hip replacement or revision of a previously inserted hip prosthesis
Exclusion criteria	Major exclusion criteria: active bleeding; contraindication to anticoagulant prophylaxis; need for ongoing anticoagulant/antiplatelet treatment (full list provided in an appendix)
Recruitment/selection of patients	Potentially eligible patients were identified during a screening period of up to 14 days before surgery and were randomly assigend to the interventions.
Age, gender and ethnicity	Age - Mean (range): Apixaban 60.9 (19-92) vs. Enoxaparin 60.6 (19-93). Gender (M:F): 2526:2881. Ethnicity: White 90.6%; Asian 6.8%; Black 2.4%; American Indian / Native Alaskan 0.06%; Hawaiian / Pacific Islander 0.02%; Other 0.07%
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=2708) Intervention 1: Apixaban - Apixaban (all doses). Orally 2.5mg twice daily. Duration 32 to 38 days. Concurrent medication/care: Placebo injections once daily to match enoxaparin (n=2699) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous injections 40mg once daily. Duration 32 to 38 days. Concurrent medication/care: Placebo tablets twice daily to match apixaban
Funding	Study funded by industry (Bristol-Myers Squibb and Pfizer)

Study	ADVANCE-3 trial: Lassen 2010[194]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN versus ENOXAPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death during treatment period at 32 to 38 days; Group 1: 3/2708, Group 2: 1/2699
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Death during follow-up period at 60 days after the end of treatment period; Group 1: 2/2598, Group 2: 1/2577
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 110, Reason: Did not complete follow-up evaluation; Group 2 Number missing: 122, Reason: Did not complete follow-up evaluation

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: All DVT during treatment period at 32 to 38 days; Group 1: 22/1944, Group 2: 68/1911
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 764, Reason: Did not have adjudicated bilateral venogram that could be evaluated or did not have adjudicated symptomatic or asymptomatic DVT; Group 2 Number missing: 788, Reason: Did not have adjudicated bilateral venogram that could be evaluated or did not have adjudicated symptomatic or asymptomatic DVT

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: All PE during treatment period at 32 to 38 days; Group 1: 3/2708, Group 2: 5/2699
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding during treatment period at 32 to 38 days; Group 1: 22/2673, Group 2: 18/2659; Comments: ARD 0.1 (95% CI -0.3 to 0.6); p=0.54
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Defined as the composite of adjudicated symptomatic or asymptomatic proximal DVT, non-fatal PE or death related to VTE; Group 1 Number missing: 35, Reason: Did not receive any study drug; Group 2 Number missing: 40, Reason: Did not receive any study drug

Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy;

Study	ADVANCE-3 trial: Lassen 2010[194]
echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE during treatment period at 32 to 38 days; Group 1: 1/2708, Group 2: 0/2699 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding during treatment period at 32 to 38 days; Group 1: 109/2673, Group 2: 120/2659; Comments: ARD -0.4 (95%CI -1.5 to 0.7); p=0.43 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Defined as the composite of adjudicated symptomatic or asymptomatic proximal DVT, non-fatal PE or death related to VTE; Group 1 Number missing: 35, Reason: Did not receive any study drug; Group 2 Number missing: 40, Reason: Did not receive any study drug Protocol outcome 7: VTE at 7-90 days from hospital discharge - Actual outcome: Major VTE during treatment period at 32 to 38 days; Group 1: 10/2199, Group 2: 25/2195; Comments: RR 0.40 (95% CI 0.15 to 0.80); ARD -0.7 (95% CI -1.3 to -0.2); p=0.01 Protocol outcome 8: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: Symptomatic DVT during follow-up period at 60 days after the end of treatment period; Group 1: 0/2598, Group 2: 3/2577 Protocol outcome 9: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 32 to 38 days; Group 1: 7/2196, Group 2: 20/2190 Protocol outcome 10: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding during treatment period at 32 to 38 days; Group 1: 0/2708, Group 2: 0/2699 Protocol outcome 11: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Surgical site bleeding at 32 to 38 days; Group 1: 18/2673, Group 2: 16/2659 - Actual outcome: Haemarthrosis in the operated joint at 32 to 38 days; Group 1: 2/2673, Group 2: 4/2659	
Protocol outcomes not reported by the study	Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Levine 1991[208]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=LMWH: 333; standard heparin: 332)
Countries and setting	Conducted in Canada; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10-14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was diagnosed using venograms
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing elective hip replacement surgery
Exclusion criteria	Less than 40 years of age; had an underlying bleeding disorder; had a history of allergy to iodine or radiopaque dye; had severe hepatic or renal disease; had had a myocardial infarction or stroke within the previous 6 months; had an underlying psychiatric or addictive disorder; or were required to receive aspirin, long-term oral anticoagulant therapy, non-steroidal anti-inflammatory medications, indomethacin, or other antiplatelet therapy during hospitalization.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH: 66.2 (10.39); Standard heparin: 66.8 (9.09). Gender (M:F): LMWH: 145/188; Standard heparin: 160/172. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=333) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 30mg twice daily (high dose) subcutaneously, from 12-24 hours after surgery continued for 14 days or until discharge if sooner. Duration 10-14 days. Concurrent medication/care: Not reported (n=332) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 7500 IU twice daily subcutaneously from 12-24 hours after surgery continued for 14 days or until discharge if sooner. Duration 10-14 days. Concurrent medication/care: Not reported
Funding	Other (Heart and Stroke Foundation of Ontario and the Medical Research Council of Canada)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus UNFRACTIONATED HEPARIN	

Study	Levine 1991[208]
(LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 10-14 days; Group 1: 50/258, Group 2: 61/263 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 75; Group 2 Number missing: 69 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 10-14 days; Group 1: 1/333, Group 2: 1/332 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 10-14 days; Group 1: 11/333, Group 2: 19/332 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT distal at 10-14 days; Group 1: 36/258, Group 2: 44/263 Protocol outcome 5: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at 10-14 days; Group 1: 14/258, Group 2: 17/263	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Manganelli 1998[213]	RCT	1+	Total: 79 randomised Intervention: n = 33 Control: n = 28 18 withdrawals (8 intervention, 10 control).	Type of surgery: Elective total hip replacement	Type: Extended duration unfractionated heparin Dose: 5000 IU Timing: 5000 IU from 1 day pre-op, every 8hrs for 30 days Additional non-comparative prophylaxis: Not reported	Type: unfractionated heparin Dose: 5000 IU Timing: 5000 IU from 1 day pre- op, every 8hrs until discharge.	Both groups: 45 days post- op	DVT Confirmed by: unilateral ascending venography on 45th day post-op (earlier if symptomatic)	Int: 4/33 Control: 6/28 p value: 0.48	Comments: Patients randomised at discharge. 2 patients had objectively confirmed PE, but the paper does not report the study group these patients were in. Not reported: PE, PTS, QoL, Survival, funding
				Intervention: Mean age: 65±8.2 yrs M/F:10/23				Proximal DVT Confirmed by: unilateral ascending venography on 45th day post-op (earlier if symptomatic)	Int: 1/33 Control: 5/28 p value: 0.08	
				Control: Mean age: 66.2±11.5 M/F:15/23				Major haemorrhage clinically overt and associated with a decrease in haemoglobin values of 2g/dl or more, compared with the last	Int: 0/33 Control: 0/33 p value: N/A	
				Pre-existing risk factors: Obesity (no significant differences between groups)						

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								post- op value, or a need for blood transfusion, or if it was retroperitoneal or intracranial		
								Length of Hospital Stay	Int: 12±2 days Control: 12±3 days p value: Not significant	

Study	Mannucci 1976[214]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=Trial 1: n=96, Trial 2: n=47)
Countries and setting	Conducted in Italy; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7-15 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 40 or more and undergoing elective operation of hip replacement for osteoarthritis or elective hip arthroplasty
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported

Study	Mannucci 1976[214]
Age, gender and ethnicity	Age - Mean (SD): Trial 1: 60.1, Trial 2: 59.4. Gender (M:F): 1:4. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=68) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U of subcutaneous heparin 2 hours preoperatively and 8 hourly postoperatively until patients were full ambulatory on crutches. Duration Not reported. Concurrent medication/care: Analgesic therapy using paracetamol or pentazocine (n=75) Intervention 2: No treatment - Usual care. No treatment. Duration Not reported. Concurrent medication/care: Analgesic therapy using paracetamol or pentazocine
Funding	Study funded by industry (Supported in part by a grant from the Fondazione Angelo Bianchi Bonomi)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at Not reported; Group 1: 14/68, Group 2: 36/75; Comments: Trial 1: UFH 9/45, Control 22/51
Trial 2: UFH 5/23, Control 14/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Surgical site haematoma at up to 45 days from hospital discharge
- Actual outcome: Wound haematoma at Not reported; Group 1: 12/68, Group 2: 1/75; Comments: Trial 1: UFH 9/45, Control 0/51
Trial 2: UFH 3/23, control 1/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: DVT (distal) at 7-90 days from hospital discharge
- Actual outcome: DVT (distal) at Not reported; Group 1: 7/68, Group 2: 25/75; Comments: Trial 1: UFH 4/45, Control 15/51
Trial 2: UFH 3/23, Control 10/24

Study	Mannucci 1976[214]
Protocol outcome 4: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at Not reported; Group 1: 7/68, Group 2: 11/75; Comments: Trial 1: UFH 5/45, Control 7/51 Trial 2: UFH 2/23, Control 4/24	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Moskovitz 1978[231]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=67)
Countries and setting	Conducted in USA; Setting: Two hospitals
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled to undergo total hip arthroplasty
Exclusion criteria	A prior history of venous thromboembolic events, a history of gastric or duodenal ulcer with heamorrhage within the previous 6 months, a positive stool guaiac, hematuria, a sensitivity to iodinated compounds, or a diastolic blood

Study	Moskovitz 1978[231]
	pressure greater than 100ml of mercury. Other reasons for exclusion were a patient's refusal to be involved and technical problems and errors in the collection of data or in the conduct of the protocol.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 46% ≥60 years; 54% <59 years. Gender (M:F): 1:1. Ethnicity: 76.1% white, 23.8% black
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH (sodium heparin), 5000U subcutaneously every 8 hours, beginning the day of surgery for a total of 21 doses (7 days). Patients wore AES (length unspecified), length of time AES worn for not reported. Duration Not reported. Concurrent medication/care: Not reported (n=32) Intervention 2: Anti-embolism stockings - Mixed above/below knee. Placebo, saline, subcutaneously given every 8 hours. Patients wore AES (length unspecified), length of time AES worn for not reported. . Duration Not reported. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus MIXED ABOVE/BELOW KNEE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Not reported; Group 1: 0/35, Group 2: 0/32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at Not reported; Group 1: 8/32, Group 2: 19/28
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4

Study	Moskovitz 1978[231]
Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 3/35, Group 2: 1/32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Not reported; Group 1: 3/35, Group 2: 0/32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at Not reported; Group 1: 4/32, Group 2: 9/28 Protocol outcome 6: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at Not reported; Group 1: 4/32, Group 2: 10/28	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Paiement 1987 [248]	RCT	1+	Total: 165 (138 completed study) Intervention: n = 66 (17 left study) Control: n = 72 (8 left study)	Type of surgery: Total hip replacement Duration of surgery not reported Intervention: Mean age: Not reported M/F:70/68 in the study. Control: Mean age: Not reported M/F:70/68 in the study.	Type: Bilateral thigh-length IPCD device Dose: 45-55 mmHg Timing: Started eve before operation. Worn continuously Additional non-comparative prophylaxis: Not reported	Type: Warfarin (low-dose) Dose: 10 mg pre-op, 5 mg post-op, thereafter adjusted to maintain PTT at 15 seconds for control at 11 - 12 seconds Timing: Started evening before operation, discontinued 2 days post phlebography if negative result	10 days	DVT Confirmed by: Venography 10th day post-op. Performed on operated limb first. If negative, contralateral limb also assessed	Int: 11/66 Control: 12/72 p value: Not significant	Comments: Patients stratified by sex and previous history of VTE prior to randomisation. 4 of 17 patients who withdrew from IPCD group did so due to intolerance of IPCD device. None of DVTs occurred in patients with previous history of VTE Not reported: PTS, LoS, QoL,
								Proximal DVT Confirmed by: Venography	Int: 9/66 Control: 4/72 p value: < 0.057	
								PE Not routinely screened for. Symptomatic PE investigated by V/Q and angiogram if high probability	Int: 0 Control: 0 p value: not reported	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
						Additional non-comparative prophylaxis: Not reported		Bleeding related complications Major bleeding (overt and associated with decrease in haemoglobin level of ≥ 2g/dl; required transfusion of 2 or more units; retroperitoneal or occurred in major prosthetic joint; intracranial); Intraoperative and post-operative blood loss (weight of sponges; suction drainage blood	Major bleeding: Int: 0/66 Control: 0/72 p value: N/A Overall blood loss for primary procedures: Int: 1821 ± 721 ml Control: 1861 ± 648 ml Not significant Revision cases Int: 3122 ± 1700 ml Control: 3218 ± 2076 ml Not significant loss; estimates of blood on wound drapes	Survival, Funding info

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Pitto 2004 [259]	RCT	1+	Total: 216 Intervention: n = 100 Control: n = 100	Type of surgery: Total hip replacement in patients with osteoarthritis Intervention: Mean age: 57.3±12 yrs M/F:30/70 Mean duration of surgery: 69+10 minutes Control: Mean age: 58.1±11 M/F:32/68 Mean duration of surgery: 65+11 minutes	Type: A-V Impulse System foot pump (slippers) and patient in Trendelenburg position (head-high, feet-low) Cycle: 130 mmHg for one second every 20 seconds Timing: (duration) started after surgery, not stated when stopped - could be used until discharge Additional non-comparative prophylaxis: Bilateral thigh-high anti-thromboembolic stockings.	Type: Low molecular weight heparin (Fraxiparin) continued after surgery Dose: adjusted to body weight, 0.2 to 0.6ml; 0.1ml = 950IU of anti Xa. Timing: started postoperatively, not stated when stopped but could be until discharge. Additional non-comparative	Control: 45 days Int: 45 days	DVT Confirmed by: serial bilateral duplex	Int: 3/97 Control: 6/94 p value: 0.30	Comments: Discrepancy with randomisation: computer generated numbers lead to 100 in each group but 216 were randomised. 16 dropped out of mechanical group because did not tolerate foot pump. Dropouts occurred between postoperative days 3 and 10. Not reported: PE, LoS, Post-thrombotic leg
								Proximal DVT Confirmed by: serial bilateral duplex	Int: 0/97 Control: 2/94 p value: 0.29	
								Distal DVT Confirmed by: serial bilateral duplex	Int: 3/97 Control: 4/94 p value: 0.67 Not significant	
								Symptomatic DVT Confirmed by: serial bilateral duplex	Int: 1/100 Control: 1/100 Not significant	
								PE Confirmed by:	Int: 0/100 Control: 0/100	
								Fatal PE Confirmed by:	Int: 0/100 Control: 0/100	
								Major bleeding from wound	Int: 0/100 Control: 0/100	
								Major	Int: 0/100	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
					Physiotherapy and mobilisation with partial weight bearing usually started on postoperative day 2. Low molecular weight heparin (Fraxiparin) administered subcutaneously 12 hours preoperatively (dose adjusted to body weight, 0.2 to 0.6ml; 0.1ml = 950IU of anti Xa).	prophylaxis: Bilateral thigh-high anti-thromboembolic stockings. Physiotherapy and mobilisation with partial weight bearing usually started on postoperative day 2. Low molecular weight heparin (Fraxiparin) administered subcutaneously 12 hours preoperatively (dose adjusted to body weight, 0.2 to 0.6ml; 0.1ml = 950IU of anti Xa).		bleeding not related to wound	Control: 0/100	Also reported: Distal DVT, minor bleeding from wound; no. of hips without bruising at days 3 & 10, no. of hips without oozing at days 3 & 10 Funding: stated that authors have or will receive benefits from a commercial party directly related to the subject of this study. Does not state who the commercial party is nor what the benefits are.
								Heparin-induced thrombocytopenia	Int: 0/100 Control: 1/100 p value not reported	
								Survival	Int: 100/100 Control: 100/100	

Study	Planès 1990[263]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=Trial 1: n=100; Trial 2: n=237)
Countries and setting	Conducted in France
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12-14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by bilateral ascending venography
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Trial 1: Consecutive people operated on for THR and iterative total hip replacement. Trial 2: Consecutive people who were 45 years of age or older, over 45kg and undergoing elective hip replacement.
Exclusion criteria	Trial 1: Not reported Trial 2: Patients younger than 45 years, under 45kg, with a past history of thromboembolism, those operated on under spinal anaesthesia, those undergoing revision hip surgery, with recent hip trauma, with thrombocytopenia, with renal insufficiency, with recent gastrointestinal bleeding, with a deficit in antithrombin III, under anticoagulant therapy or with an activated partial thromboplastin time (APTT) 10 sec longer than the control, under antiplatelet therapy during the 8 days prior to surgery, with an iodine sensitivity, and those who refused informed consent for the study or the phlebography.
Recruitment/selection of patients	Consecutive recruitment
Age, gender and ethnicity	Age - Other: Trail 1 (mean): 65; Trial 2 (age ± SD): Group A: 63.08 ± 9.52; Group B: 64.44 ± 9.62. Gender (M:F): Trial 1: 1:1; Trial 2: Not reported. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 40mg once daily (standard dose) subcutaneously from 12 hours pre-operation. Duration Duration unclear, possibly until discharge. Concurrent medication/care: Not reported (n=78) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 60mg once daily (high dose) subcutaneously from 12 hours pre-operation. Duration Duration of intervention unclear, possibly until discharge. Concurrent medication/care: Not reported

Study	Planès 1990[263]
	(n=124) Intervention 3: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 40mg once daily (standard dose) subcutaneously from 12 hours preoperatively for 14 days or until hospital discharge. Duration Unclear. Concurrent medication/care: Not reported (n=113) Intervention 4: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Calcium heparin, 5000 IU subcutaneously every 8 hours from 2 hours pre-operation for 14 days or until hospital discharge. Duration 14 days. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 12-15 days; Group 1: 12/150, Group 2: 5/78
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Surgical site haematoma at up to 45 days from hospital discharge
- Actual outcome: Wound haematoma at 12-15 days; Group 1: 3/50, Group 2: 6/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 100; Group 2 Number missing: 28

Protocol outcome 3: DVT (distal) at 7-90 days from hospital discharge
- Actual outcome: DVT distal at 12-15 days; Group 1: 4/150, Group 2: 2/28

Protocol outcome 4: DVT (proximal) at 7-90 days from hospital discharge
- Actual outcome: DVT proximal at 12-15 days; Group 1: 8/150, Group 2: 3/28

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler)

Study	Planès 1990[263]
ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Unclear; Group 1: 15/120, Group 2: 27/106 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7 - Actual outcome: DVT at Unclear; Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Unclear; Group 1: 0/120, Group 2: 1/106 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7 Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Unclear; Group 1: 2/120, Group 2: 0/106 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7 Protocol outcome 4: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT distal at Unclear; Group 1: 6/120, Group 2: 7/106 Protocol outcome 5: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at Unclear; Group 1: 9/120, Group 2: 20/106	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Planes 1996[262]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=179)
Countries and setting	Conducted in France; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 19-23 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by bilateral phlebographic examination. PE confirmed by pulmonary angiography or by autopsy. Major bleeding defined as overt and associated with either a fall in haemoglobin level of ≥20g/L or a need for transfusion of 2 or more units of blood, or if it was retroperitoneal or intracranial.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People considered for the study were aged more than 45 years, weighed between 45 and 95 kilograms, had undergone primary THR and received enoxaparin as prophylaxis for postoperative venous thromboembolism while hospitalised. Patients could be included if after surgery, they could walk with the help of crutches - but otherwise unassisted - using the operated leg to give firm support, and if they were free of DVT as assessed by an initial bilateral ascending venography performed within the 5 days prior to discharge.
Exclusion criteria	History of documented thromboembolism during the last 6 months; cancer in progression; an underlying bleeding disorder or an abnormality in haemostasis (such as platelet count < 100 000/mm³, a prothrombin INR of > 1.5, or an activated prothrombin time > 8 seconds longer than that of control), or active gastroduodenal ulcer; a known allergy to heparin or contrast media; renal or hepatic insufficiency; uncontrolled arterial hypertension; recent stroke; or inability to give informed consent.
Recruitment/selection of patients	Consecutive recruitment
Age, gender and ethnicity	Age - Mean (SD): LMWH: 70 (9.1); Placebo: 68 (8.2). Gender (M:F): LMWH: 47/43; Placebo: 55/34. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=90) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 40mg once daily (standard dose), subcutaneously from 12 hours pre-operatively, 12 hours postoperatively, until 21±2 days (extended duration). Duration 21±2 days. Concurrent medication/care: Patients were advised to wear

	elastic bandages/AES on both legs (% of patients that used AES not reported), avoid other anticoagulant treatment, aspirin, ticlopidine and NSAIDs (n=89) Intervention 2: No treatment - Placebo. Isotonic saline 0.4ml. Duration 21±2 days. Concurrent medication/care: Patients were advised to wear elastic bandages/AES on both legs (% of patients that used AES not reported), avoid other anticoagulant treatment, aspirin, ticlopidine and NSAIDs
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 19-23 days; Group 1: 0/90, Group 2: 0/89
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 19-23 days; Group 1: 6/85, Group 2: 17/88
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 1

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 19-23 days; Group 1: 0/90, Group 2: 0/89
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 19-23 days; Group 1: 0/90, Group 2: 0/89
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Wound haematoma at 19-23 days; Group 1: 1/90, Group 2: 1/89 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT distal at 19-23 days; Group 1: 1/85, Group 2: 10/88 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at 19-23 days; Group 1: 5/85, Group 2: 7/88	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	**Prandoni 2002[266]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=360)
Countries and setting	Conducted in Italy; Setting: University of Padua, Italy
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 4 weeks post-discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by compression ultrasound or intraluminal filling defect on ascending phlebography PE : confirmed by a high-probability ventilation-perfusion lung scan, a spiral computed tomographic scan, or an abnormal finding on angiography or (in case of death) autopsy. Major bleeding: defined as clinically overt and associated with either a decrease in haemoglobin of at least 2.9 g/dL or

Study	Prandoni 2002[266]
	a need for a transfusion of 2 of more units of red blood cells, was intracranial or retroperitoneal or resulted in the permanent discontinuation of anticoagulation.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients who underwent elective total hip arthroplasty and received warfarin prophylaxis during hospitalisation were potentially eligible for the study provided they had not undergone previous hip surgery on the same side or did not have a history of thromboembolic disorders.
Exclusion criteria	Eligible patients were excluded from the study if they developed venous thromboembolic complications or major bleeding during hospitalisation. Patients with asymptomatic proximal DVT, as shown by a bilateral compression ultrasound examination performed before hospital discharge were also excluded as were those who needed long-term anticoagulation, were unavailable for long-term follow-up or refused to give their written informed consent.
Recruitment/selection of patients	From September 1998 to December 2000
Age, gender and ethnicity	Age - Median (range): 69 (44-87). Gender (M:F): 1/1.2. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Extra comments	Length of hospitalisation (median): 9 days for both groups
Indirectness of population	No indirectness
Interventions	(n=184) Intervention 1: Vitamin K antagonists - Warfarin (all doses). Patients received 5 mg/d of sodium warfarin starting on the second preoperative day; after the intervention, the dosage was adjusted to increase the INR between 2.0 to 3.0. Duration 4 weeks post-discharge. Concurrent medication/care: n/a (n=176) Intervention 2: Vitamin K antagonists - Warfarin (all doses). Patients received 5 mg/d of sodium warfarin starting on the second preoperative day; after the intervention, the dosage was adjusted to increase the INR between 2.0 to 3.0. Duration Intervention stopped at discharge. Concurrent medication/care: n/a
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN (EXTENDED DURATION) versus WARFARIN (STANDARD DURATION)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 28 days; Group 1: 0/184, Group 2: 0/176
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Study	Prandoni 2002[266]
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 28 days; Group 1: 3/184, Group 2: 8/176 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 28 days; Group 1: 0/184, Group 2: 1/176 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 28 days; Group 1: 1/184, Group 2: 0/176 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Samama 1997[281]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=170)

Study	Samama 1997[281]
Countries and setting	Conducted in France; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12-90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by ultrasonography or venography. PE confirmed by ventilation-perfusion lung scan or angiography.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive people aged more than 18 tears, weighing 45-95kg, undergoing primary THR surgery under regional anaesthesia (subarachnoid block and catheter removed at the end of the surgical procedure), wearing gradual compression stockings (started the day before surgery).
Exclusion criteria	Re-operation for THR, surgery under general anaesthesia, patients under nail extension before surgery, history of DVT, pulmoanry embolism, or both, hepatic or renal insufficicency, lung or heart failure, ASA status more than III, haemorrhagic disorders contraindicating the use of antithrombotic drugs (active ulcerative disease, uncontrolled arterial hypertension, stroke within the previous 6 months or other known haemorrhagic disorders), occurence of a bloody tap during spinal puncture, platelet count less than 100x10^9 litre^-1, history of heparin-associated thrombocytopenia or allergic reactions to heparin, low molecular weight heparin or to radiocontrast agents, and women with childbearing potential. In addition patients were excluded if they received heparin for more than 24 hours before surgey, oral anticoagulant treatment within 3 days, antiplatelet drugs within 8 days or non-steroidal anti-inflammatory agents within 2 days before surgery.
Recruitment/selection of patients	Consecutive recruitment
Age, gender and ethnicity	Age - Mean (range): LMWH: 67.2 (36.9-89.21); Placebo: 67.2 (31.6-87.5). Gender (M:F): LMWH: 58/27; Placebo: 41/44. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=85) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 40mg once daily (standard dose) subcutaneously . Duration administered for 10±2 days. Concurrent medication/care: AES (n=85) Intervention 2: No treatment - Placebo. Sodium chloride saline. Duration administered for 10±2 days. Concurrent medication/care: AES

Study	Samama 1997[281]
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 90 days; Group 1: 0/78, Group 2: 0/75
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 10

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 12 days; Group 1: 11/78, Group 2: 28/75
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 10

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 90 days; Group 1: 0/78, Group 2: 0/75
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 10

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding defined as overt and associated with either a decrease in haemoglobin of 2g/dl or more, a need for transfusion of 2 units or more of packed red blood cells, if it was retroperitoneal or intracranial, or if it led to sugical re-intervention or death at 12 days; Group 1: 1/78, Group 2: 1/75
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 10

Protocol outcome 5: Surgical site haematoma at up to 45 days from hospital discharge
- Actual outcome: Wound haematoma at 12 days; Group 1: 33/78, Group 2: 20/75
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 10

Study	Samama 1997[281]
Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT distal at 12 days; Group 1: 8/78, Group 2: 13/75 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at 12 days; Group 1: 2/78, Group 2: 12/75	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Samama 2002[283]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1289)
Countries and setting	Conducted in France; Setting: Multicentre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 42-63 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients 18 years or older scheduled to undergo elective unilateral primary total hip replacement surgery who gave informed consent
Exclusion criteria	Femoral neck fracture; current active bleeding or disorders contraindicating anticoagulant therapy; a history of DVT or PE; heparin induced thrombocytopenia; peptic ulcer; allergy to radiopaque contrast medium; use of aspirin or ticlopidine hydrochloride, renal insufficiency, liver failure; acute endocarditis; recent stroke; uncontrolled hypertension; pregnancy; alcoholism; or inability to follow instructions
Recruitment/selection of patients	Consecutive patients

Study	Samama 2002[283]
Age, gender and ethnicity	Age - Mean (SD): Reviparin group: 66 (11), Acenocoumarol group: 65 (12). Gender (M:F): 1:1. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean (SD) BMI = 27 (4)). 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=644) Intervention 1: Low molecular weight heparin (not licensed in UK) - Reviparin (1750 units once daily - 4200 units once daily). Reviparin, 4200IU once daily (high dose) subcutaneously, initial dose 12 hours preoperatively for 3±1 days, continued for 6 weeks (extended duration). Duration 6 weeks. Concurrent medication/care: n/a (n=645) Intervention 2: Vitamin K antagonists - Acenocoumarol (all doses). Patients given initial dose of reviparin, 4200IU (high dose) 12 hours preoperatively, crossed over to acenocoumarol for 6 weeks after surgery (extended duration). The dose was adjusted to achieve an INR between 2.0 and 3.0 for 2 consecutive days. Duration 6 weeks. Concurrent medication/care: n/a
Funding	Study funded by industry (Supported by Knoll-France, Levallois-Perret France. The local investigators received $400 per patients included in the study, and the institution of the investigator in chief received a final grant of $4000)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REVIPARIN (EXTENDED DURATION) versus ACENOCOUMAROL/VKA (EXTENDED DURATION)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 42-63 days; Group 1: 0/643, Group 2: 2/636
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Details not reported; Group 2 Number missing: 9, Reason: Details not reported

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 42-63 days; Group 1: 15/643, Group 2: 20/636
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Details not reported; Group 2 Number missing: 9, Reason: Details not reported

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 42-63 days; Group 1: 0/643, Group 2: 4/636
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Details not reported; Group 2 Number missing: 9, Reason: Details not reported

Study	Samama 2002[283]
Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 42-63 days; Group 1: 10/643, Group 2: 37/636 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Details not reported; Group 2 Number missing: 9, Reason: Details not reported	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Santori 1994 [288]	RCT	1+	Total: n = 132 Intervention : n = 67 Control:	Type of surgery: Patients undergoing total hip replacement. All patients had compression	Intermittent plantar foot pump (aka impulse group) on both feet immediately after	Calcium heparin. 5000 Units 3x per day for 10 days starting on the	Intervention for 8 to 10 days, follow-up 6	DVT (overall) Confirmed by: thermography and doppler US followed by phlebography	Int: 9/67 Control: 23/65 p value: <0.005	The paper did not report any dropouts 2 PEs (1 fatal) in the heparin

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			n = 65	stockings after operation Excluded: history of VTE, varicose veins, venous insufficiency in the legs, malignant neoplasm Intervention: Mean age: 72.4±6.65	the operation and used for 7 to 10 days. When patients started walking at postoperative day 4 or 5 the foot pump was only used when the patient was in	day before the operation Additional prophylaxis: AES on both legs after operation. Neither the length nor for how long they were worn was	weeks	"Major" proximal DVTs	Int: 2/67 Control: 11/65 p value: : 0.0083	group but not stated how confirmed Not reported: PTS, PE, QoL, Survival
								"Major" proximal & distal DVTs	Int: 0/67 Control: 2/65 p value: : 0.2406	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				M/F:19/48 Control Mean age: 69.8±6.22 M/F:15/50 Pre-existing risk factors: Not reported	bed. Additional prophylaxis: AES on both legs after operation. Neither the length nor for how long they were worn was stated. Physiotherapy with mobilisation started on 2nd postoperative day. Walking began on 4th or 5th postoperative day	stated. Physiotherapy with mobilisation started on 2nd postoperative day. Walking began on 4th or 5th postoperative day		Mean +SD total blood loss (ml)	Int: 490 +195.27 (n = 67) Control: 520 +189.16 (n = 65) P value: not reported	
								Mean +SD volume of blood transfused (ml)	Int: 308 +289.15 (n = 67) Control: 300 +267.7 (n = 65) P value: not reported	

Study	Tørholm 1991[313]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=112)
Countries and setting	Conducted in Denmark; Setting: Rigshospitalet University Hospital of Copenhagen
Line of therapy	Not applicable
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by 125I fibrinogen test and ascending phlebography.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who were admitted for THR and who were aged 40 years or over were eligible.
Exclusion criteria	Bleeding disorders, hepatic or renal insufficiency, previous septic endocarditis, cerebral haemorrhage during the previous six months, hypersensitivity to heparin or iodine, and anticoagulant therapy within one week of surgery.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (IQR): Fragmin: 67 (43-85); Placebo: 64 (43-81). Gender (M:F): Fragmin: 23/35; Placebo: 27/27. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). LMWH Dalteparin, 2500 IU subcutaneously for the first two doses (2 hours before surgery and 12 hours postoperatively), then 5000 IU subcutaneously for the following six days. Duration 9 days. Concurrent medication/care: Not reported (n=54) Intervention 2: No treatment - Placebo. Sodium chloride 9g/l subcutaneously using same regimen as intervention group. Duration 9 days. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge

Study	Tørholm 1991[313]
- Actual outcome: All-cause mortality at Time point not reported; Group 1: 1/58, Group 2: 0/54 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 9 days; Group 1: 9/58, Group 2: 19/54 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Time point not reported; Group 1: 0/58, Group 2: 1/54 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Infection at duration of study - Actual outcome: Wound infection at Time point not reported; Group 1: 2/58, Group 2: 0/54 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT distal at 9 days; Group 1: 9/58, Group 2: 14/54 Protocol outcome 6: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at 9 days; Group 1: 0/58, Group 2: 5/54	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital

Study	Tørholm 1991[313]
	discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Turpie 1986[318]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=LMWH: 50; Placebo: 50)
Countries and setting	Conducted in Canada; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by venography or 125I fibrinogen scanning. Major bleeding defined as overt and associated with either a fall in the heamoglobin level of 2g/dl or more, or a need for transfusion of two or more units of blood, or if it was retroperitoneal or intracranial.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	People were recruited consecutively
Age, gender and ethnicity	Age - Mean (SD): LMWH: 66.82 (9.55); Placebo: 67.3 (8.85). Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 30mg twice daily (high dose) subcutaneously, from 12 to 24 hours after surgery for 14 days or until discharge. Duration 14 days. Concurrent medication/care: Not reported (n=50) Intervention 2: No treatment - Placebo. 0.3 ml saline, subcutaneously from 12 to 24 hours after surgery for 14 days. Duration 14 days. Concurrent medication/care: Not reported

Study	Turpie 1986[318]
Funding	Academic or government funding (Supported by grants from the Heart and Stroke Foundation of Ontario and the Medical Research Council of Canada)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 14 days; Group 1: 0/50, Group 2: 1/50
Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 14 days; Group 1: 4/37, Group 2: 20/39
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 11

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 14 days; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 14 days; Group 1: 1/50, Group 2: 2/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: DVT (distal) at 7-90 days from hospital discharge
- Actual outcome: DVT distal at 14 days; Group 1: 2/37, Group 2: 11/39

Protocol outcome 6: DVT (proximal) at 7-90 days from hospital discharge
- Actual outcome: DVT proximal at 14 days; Group 1: 2/37, Group 2: 9/39

Study	Turpie 1986[318]
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Turpie 2002[319]	RCT	1+	Total: 2275 Intervention n: 1138 Control n: 1137 Dropouts (not treated): Int: 10 Comp: 8 Dropout	Type of surgery: Patients scheduled for primary elective total hip-replacement surgery or revision of at least one component of a previously implanted total hip prosthesis. Duration of surgery:	2.5 mg of Fondaparinux sodium and a placebo. The first active dose was given 4-8 hrs after surgery and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day	30 mg of Enoxaparin twice daily. The first active dose was given 4-8 hrs after surgery and the second 12 or more after the first. Treatment was scheduled to continue until	49 days study period 11 days	DVT Confirmed by: systematic bilateral ascending venography	Int: 44/784 Control: 65/796 p value: <0.047; RRR:- 31.3% (95% CI)	Funding: study supported by NV Organon and Sanofi-Synthelabo. ** defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any
								VTE	Int: 48/787 Control: 66/797 p value: 0.099 RRR (95 % CI) -26.3 (-52.8 to -10.8)	
								Symptomatic DVT	Int: 5/1126 Control: 0/1128 p value: 0.0310	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			s (not available for analysis): Int: 341 Comp: 332	2.42 hours, SD: ±0.98 Intervention: Mean age: 67, range: 26-92; M/F:386/401 Control: Mean age: 67, range: 19-91; M/F:375/422 Pre-existing risk factors: History of VTE: Intervention: 40 (5%) Control: 50 (6%). Orthopaedic surgery within the previous 12 months: Intervention: 99 (13%) Control: 84 (11%)	of surgery is day 1. Additional non-comparative prophylaxis: The use of AES and physiotherapy was recommended No. patients receiving/using: AES = 674/787 Anticoagulant/antiplat elet therapy (not aspirin) = 13/787 NSAIDs or aspirin = 107/787	day 5 to 9. Day of surgery is day 1. Additional non-comparative prophylaxis: The use of AES and physiotherapy was recommended No. patients receiving/using: AES = 676/797 Anticoagulant/antiplatelet therapy(not aspirin) = 11/797 NSAIDs or aspirin = 108/797		Proximal DVT* Confirmed by: systematic bilateral ascending venography	Int: 14/816 Control: 10/830 p value: 0.42	other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								Non-fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	Int: 5/1126 Control: 0/1128 p value: 0.0310	
								Fatal PE Confirmed by:	Int: 0/1126 Control: 1/1128 p value: 1.0000	
								Major bleeding **	Int: 20/1128 Control: 11/1129 p value: 0.73	
								Fatal bleeding	Int: 0/1128 Control: 0/1129 p value: 1.0000	
								Bleeding leading	Int: 2/1128	

Study	Warwick 1995 [332]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=156)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8-10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by ipsilateral venography. PE confirmed by ventilation/perfusion scan.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People have a primary THR
Exclusion criteria	Recent aspirin consumption, a medical requirement for continued non-steroidal medication, and a history of previous thromboembolism.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - --: Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=78) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 40mg once daily (standard dose) subcutaneously administered from 12 hours before operation, then at 12 hours and 36 hours postoperatively. AES bilateral thigh length stockings also used. Duration 8-10 days. Concurrent medication/care: All patients were mobilised on the second postoperative day (n=78) Intervention 2: Anti-embolism stockings - Above knee. AES, bilateral thigh length alone. Duration 8-10 days. Concurrent medication/care: All patients were mobilised on the second postoperative day
Funding	Other (Wishbone Trust, teh Laming Evans Orthopaedic Fellowship and the South West Regional Health Authority

Study	Warwick 1995 [332]
	Research Committee)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus ABOVE KNEE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at not specified; Group 1: 22/78, Group 2: 33/78 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 8-10 days; Group 1: 1/78, Group 2: 2/78 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT proximal at not specified; Group 1: 12/78, Group 2: 14/78	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Warwick 1998[333]	RCT	1+	Total: n = 290 Intervention: n = 147 Control: n = 143	Type of surgery: Patients undergoing total hip replacement Intervention: Mean age: 68±11 M/F:94/53 Pre-existing risk factors: Previous thomboembolism: Int: n = 2, control:n = 3	foot pump for 7days	Enoxaparin Dose: 40mg/daily for 7 days Timing: 7days Additional prophylaxis: Not reported	Control: 3mths Int: 3mths	DVT (overall) Confirmed by:venography on 6th, 7th & 8th day	Int: 24/136 Control: 18/138 (95%CI, -3.9 to +13.0%) p value: Not significant	Comments: 136 patients in the intervention and 138 in the comparison group completed both venography and the 3 month follow-up No patient died during follow-up Not reported: PTS, Bleeding related complications, QoL, Survival Also reported: Intraoperative blood loss, postop
								Proximal vein thrombosis	Int: 17/136 Control: 12/138 (95%CI, -3.5 to +11.1%) p value: Not significant	
								Distal vein thrombosis	Int: 7/136 Control: 6/138 (95%CI, -4.2 to +5.8%) p value: Not significant	
								Symptomatic PE Confirmed by ventilation perfusion scanning	Int: 1/136 Control: 0/138 p value: Not significant	
								Fatal PE Confirmed by:	Int: 0/136 Control: 0/138 p value: Not significant	
								Readmission to hospital	Int: 1/136 Control: 1/138 p	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								because of DVT:	value: Not significant	drainage, median no. of units transfused, oozing and bruising of thigh

Study	Yokote 2011[347]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=255)
Countries and setting	Conducted in Japan; Setting: Nissan Tamagawa Hospital, Tokyo, Japan
Line of therapy	Not applicable
Duration of study	Intervention time: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by duplex ultrasonography PE: confirmed by multi-detector CT scan Major bleeding: defined as retroperitoneal, intracranial or intraocular bleeding, or if it was associated with either death, transfusion or more than two units of packed red blood cells or whole blood (except autologous), a reduction in the level of haemoglobin of > 2g/dl, or a serious life-threatening clinical event requiring medical intervention.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing elective primary unilateral total hip replacement (THR).
Exclusion criteria	Patients who had undergone bilateral and revision total hip replacement and those who were less than 20 years of age. Other exclusion criteria included long-term anticoagulation treatment such as unfractionated heparin, low-molecular-weight-heparin, vitamin-K antagonists, antiplatelet agents for pre-existing cardiac or cerebrovascular disease, a history of VTE, a coagulation disorder including antiphospholipid syndrome, the presence of a solid

Study	Yokote 2011[347]
	malignant tumour or a peptic ulcer, and major surgery in the preceding three months. Caucasian patients were also excluded
Recruitment/selection of patients	Between May 2008 and March 2007, consecutive patients undergoing elective primary unilateral THR.
Age, gender and ethnicity	Age - Mean (SD): 64 years. Gender (M:F): 1/4. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI: 22.9 kg/m2). 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=86) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin, 40 mg (20mg twice daily) subcutaneously. AES, thigh-length and IPCD was applied in the operating theatre before the procedure until post-operative day 2. Duration 10 days. Concurrent medication/care: All patients began mobilisation exercises under the supervision of a physiotherapist within 24 hours (1 to 20 hours) after surgery. NSAIDs were given post-operatively for control of pain according to each individual patient's requirements. (n=85) Intervention 2: Fondaparinux - Fondaparinux (all doses). Fondaparinux, 2.5mg once daily, subcutaneously given. AES, thigh-length and IPCD was applied in the operating theatre before the procedure until post-operative day 2. Duration 10 days. Concurrent medication/care: All patients began mobilisation exercises under the supervision of a physiotherapist within 24 hours (1 to 20 hours) after surgery. NSAIDs were given post-operatively for control of pain according to each individual patient's requirements. (n=85) Intervention 3: No treatment - Placebo. Placebo, isotonic saline, 0.5 ml, subcutaneously given post-operation. AES, thigh-length and IPCD was applied in the operating theatre before the procedure until post-operative day 2. Duration 10 days. Concurrent medication/care: All patients began mobilisation exercises under the supervision of a physiotherapist within 24 hours (1 to 20 hours) after surgery. NSAIDs were given post-operatively for control of pain according to each individual patient's requirements.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN + IPCD + AES versus FONDAPARINUX + IPCD + AES

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 11 days; Group 1: 5/83, Group 2: 6/84
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Missed ultrasound; Group 2 Number missing: 1, Reason: Missed ultrasound

Study	Yokote 2011[347]
	Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 11 days; Group 1: 0/83, Group 2: 0/84 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Missed ultrasound; Group 2 Number missing: 1, Reason: Missed ultrasound Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 11 days; Group 1: 0/83, Group 2: 0/84 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Missed ultrasound; Group 2 Number missing: 1, Reason: Missed ultrasound Protocol outcome 4: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Wound haematoma (maximum size >5cm) at 11 days; Group 1: 3/83, Group 2: 3/84 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Missed ultrasound; Group 2 Number missing: 1, Reason: Missed ultrasound Protocol outcome 5: VTE at 7-90 days from hospital discharge - Actual outcome: VTE at 11 days; Group 1: 5/83, Group 2: 6/84 Protocol outcome 6: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 11 days; Group 1: 0/83, Group 2: 1/84 Protocol outcome 7: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 11 days; Group 1: 6/84, Group 2: 6/83 Protocol outcome 8: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 11 days; Group 1: 0/83, Group 2: 1/84 Protocol outcome 9: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Upper gastrointestinal bleeding at 11 days; Group 1: 0/85, Group 2: 2/85

Study	Yokote 2011[347]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN + IPCD + AES versus PLACEBO + IPCD + AES Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 11 days; Group 1: 5/83, Group 2: 6/83 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Missed ultrasound; Group 2 Number missing: 2, Reason: Missed ultrasound Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 11 days; Group 1: 0/83, Group 2: 0/83 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Missed ultrasound; Group 2 Number missing: 2, Reason: Missed ultrasound Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 11 days; Group 1: 0/83, Group 2: 0/83 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Missed ultrasound; Group 2 Number missing: 2, Reason: Missed ultrasound Protocol outcome 4: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Wound haematoma (maximum size >5cm) at 11 days; Group 1: 3/83, Group 2: 1/83 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Missed ultrasound; Group 2 Number missing: 2, Reason: Missed ultrasound Protocol outcome 5: VTE at 7-90 days from hospital discharge - Actual outcome: VTE at 11 days; Group 1: 5/83, Group 2: 6/83 Protocol outcome 6: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 11 days; Group 1: 0/83, Group 2: 0/83 Protocol outcome 7: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 11 days; Group 1: 5/83, Group 2: 6/83	

Study	Yokote 2011[347]
Protocol outcome 8: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 11 days; Group 1: 0/83, Group 2: 0/83 Protocol outcome 9: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Upper gastrointestinal bleeding at 11 days; Group 1: 0/85, Group 2: 1/85 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX + IPCD + AES versus PLACEBO + IPCD + AES Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 11 days; Group 1: 6/84, Group 2: 6/83 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Missed ultrasound; Group 2 Number missing: 2, Reason: Missed ultrasound Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 11 days; Group 1: 0/84, Group 2: 0/83 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Missed ultrasound; Group 2 Number missing: 2, Reason: Missed ultrasound Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 11 days; Group 1: 0/84, Group 2: 0/83 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Missed ultrasound; Group 2 Number missing: 2, Reason: Missed ultrasound Protocol outcome 4: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Wound haematoma (maximum size >5 cm) at 11 days; Group 1: 3/84, Group 2: 1/83 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Missed ultrasound; Group 2 Number missing: 2, Reason: Missed ultrasound Protocol outcome 5: VTE at 7-90 days from hospital discharge - Actual outcome: VTE at 11 days; Group 1: 6/84, Group 2: 6/83	

Study	Yokote 2011[347]
Protocol outcome 6: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 11 days; Group 1: 1/84, Group 2: 0/83 Protocol outcome 7: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 11 days; Group 1: 6/84, Group 2: 6/83 Protocol outcome 8: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 11 days; Group 1: 1/84, Group 2: 0/83 Protocol outcome 9: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Upper gastrointestinal bleeding at 11 days; Group 1: 2/85, Group 2: 1/85	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Zanasi 1988 [348]	RCT	1+	Total 63 Intervention : n = 19 Control: n = 25 (3rd arm	Type of surgery: Orthopaedic surgery (majority hip surgery) Intervention: Mean +SEM age: 69.7 +3.7 yrs	Type: aspirin: Dose: acetylsalicylic acid 100mg administered on alternate days Timing: started day	Type: unfractionated heparin: Dose: beef lung heparin 5000 units + placebo aspirin Timing: started day before	7 Post-operative days	DVT Confirmed by: FUT	Int: 7/19 Control: 10/25 p value: 0.4821	Comments: Diagnosis of DVT by ultrasonic doppler detectors in this study only permitted analysis of DVTs above the knee

			of 19 patients receiving defibrotide not reported here)	M/F: 5/14 Control: Mean +SEM age: 71.9 +2.2 yrs M/F:4/21 Pre-existing risk factors: none stated	before surgery and continued for 7 postoperative days. Additional non-comparative prophylaxis: none stated	surgery and continued for 7 postoperative days Additional non-comparative prophylaxis: none stated				Not reported PTS, QoL, bleeding complications, length of hospital stay Funding: not reported

H.24 Elective knee replacement

Study	Alkire 2010[3]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=65)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 3 days + Follow-up 3 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Computer-assisted TKA patients with a diagnosis of rheumatoid or osteoarthritis aged greater than 18 years
Exclusion criteria	Cognitive/Sensory deficits; residence in skilled nursing facilities; non-English speaking
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Other: Intervention mean age 65.6 years vs. Control mean age 66.9 years. Gender (M:F): 26:38 (one person missing due to withdrawal from the intervention group after randomisation). Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI 26 kg/m2). 2. Renal impairment: Not applicable

Study	Alkire 2010[3]
Indirectness of population	Very serious indirectness: [1] Ambiguous statements regarding the number of patients enrolled / randomised. [2] Ethnicity of the participants is not reported. [3] Following a preliminary study, the protocol for the study was amended to allow participation of patients with comorbidities, such as DVT requiring anticoagulants, weighing >240lb, and presence of other conditions such as diabetes, hypertension, stroke and lupus.
Interventions	(n=33) Intervention 1: Continuous passive motion. Danniflex 480 CPM apparatus; starting with flexion at 90 to 70 degrees in the post-anaesthesia care unit and increasing extension by 10 degrees over 4 hrs for a total of 6 hrs per day; 3 times daily for 3 days. Duration 3 days. Concurrent medication/care: Not stated Comments: Unclear if the number of participants randomised to this group is 33, 34 or 36 (descriptions given are unclear) (n=32) Intervention 2: No treatment - Usual care. Twice daily physiotherapy. Duration 3 days (implicitly assumed but not clearly stated) or until discharge ("during their hospital stay"). Concurrent medication/care: Not stated Comments: Physiotherapy given was not described in any detail.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONTINUOUS PASSIVE MOTION versus NO CPM Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 3 months; Group 1: 0/33, Group 2: 0/32; Comments: The study only stated that there were no reports of DVT. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - The definition, assessment method and time points for data collection for DVT are not reported. The participants' baseline risks for VTE (e.g. ethnicity, previous VTE, co-morbidities, medications) are not reported. Statements about the number of people enrolled, randomised and withdrawn are unclear and the exact number "randomised" cannot be established with certainty.; Indirectness of outcome: Serious indirectness ; Baseline details: Insufficient reporting of the participants' biometrics (e.g. BMI), co-morbidities, history of VTE, etc.; Blinding details: Not possible to blind participants for CPM device nor physiotherapy; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of

Study	Alkire 2010[3]
	≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bauer et al., 2001[17]	RCT	1+	Total: 1049 Intervention n: 526 Control: 523 Dropouts (not treated): Int: 9 Comp: 6 Dropout	Type of surgery: Patients undergoing elective major knee surgery. Duration of surgery: 128 minutes, SD: ±42 Intervention: Mean age: 67.5, SD: ±10.7; M/F:204/313	2.5 mg of Fondaparinux sodium postoperatively once daily and a placebo once daily subcutaneously till day 5 to 9. Day of surgery is day 1. Additional non-comparative	30 mg of Enoxaparin twice daily post-operatively until day 5 to 9. Day of surgery is day 1. Additional non-comparative prophylaxis:	49 days	DVT Confirmed by: systematic bilateral ascending venography	Int: 45/361 Control: 98/361 p value: 0.001; RR: 54.1% (95% CI)	Funding: The authors have served as consultants to NV Organon and Sanofi-Synthelabo and the study supported by NVO & SS. ** defined as fatal
								VTE	Int: 45/361 Control: 101/363 p value: <0.001 Reduction in risk (95% CI) 55.2 (36.2 to 70.2)	
								Symptomatic DVT	Int: 3/517 Control: 4/517 p value: 1.000	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			s (not available for analysis): Int: 156 Comp: 154	Control: Mean age: 67.5, SD: ±10.2; M/F:223/294 Pre-existing risk Factors: History of VTE: Intervention: 23% Control: 28%. Orthopaedic surgery within the previous 12 months: Intervention: :87% Control:: 27%	prophylaxis: The use of AES and physiotherapy was recommended No. patients receiving/using: AES = 298/361 Anticoagulant/ antiplatelet therapy (not aspirin) = 4/361 NSAIDs or aspirin= 44/361	The use of AES and physiotherapy was recommended No. patients receiving/using: AES = 294/363 Anticoagulant /antiplatelet therapy (not aspirin) = 11/363 NSAIDs or aspirin= 60/363		Proximal DVT Confirmed by: systematic bilateral ascending venography	Int: 9/368 Control: 20/372 p value: 0.06	bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								Non-fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	Int: 1/517 Control: 4/517 p value: 0.3738	
								Fatal PE Confirmed by:	Int: 0/517 Control: 0/517 p value: N/A	
								Major bleeding **	Int: 11/517 Control: 1/517 p value: 0.003	
								Bleeding leading to re-operation	Int: 2/517 Control: 1/517 p value: 1.000	
								Other bleeding – number (%)	Int: 14/517 Control: 19/517 p value: 0.4797	
								Post-operative transfusions –	Int: 222/517	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								number (%)	Control: 197/517 p value: 0.1284	
								Death from any cause - number (%) Up to day 11	Int: 1/517 Control: 2/517 p value: 1.0000	
								Death from any cause - number (%) Up to day 49	Int: 2/517 Control: 3/517 p value: 1.0000	

Study	Bern 2015[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=118)
Countries and setting	Conducted in USA; Setting: New England Baptist Hospital, Boston, USA
Line of therapy	Not applicable
Duration of study	Intervention time: 26-30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by bilateral duplex sonography PE: confirmed by ventilation/perfusion lung scan or computerised axial tomography angiogram

Study	Bern 2015[28]
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were recruited from among over 20 years of age planning elective primary unilateral total hip or knee replacement surgery at an orthopaedic surgery.
Exclusion criteria	Abnormal platelet count, pro-thombin time or partial thromboplastin time; surgery for acute fracture (<4 weeks), septic joint, or extraction arthroplasty; history of VTE or documented hyper-coagulation syndrome; increased risk of haemorrhage, as from active gastric ulcer or urinary tract bleed within the last year; haemorrhagic stroke, brain, spinal, or ophthalmologic surgery in previous 6 months; liver enzymes or bilirubin greater than 2 x normal; decreased renal function with GFR <30 ml/min; cancer in last year, other than localised cancers of the skin; requires chronic anticoagulation; requires chronic platelet function suppressive therapy; prior adverse reaction to any of the study drugs; uncontrolled hypertension; BMI >42, pregnancy
Recruitment/selection of patients	Based on inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): 60 (7.7) years . Gender (M:F): 1/1. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Fondaparinux - Fondaparinux (all doses). 2.5mg daily starting 6 or more hours following surgery, but no later than 6am the next day, or 6-8 hours after epidural catheter removal. All patients wore pneumatic compression stockings while in-patient. AES were prescribed to be used after discharge until the follow-up ultrasounds. Duration 28±2 days. Concurrent medication/care: Use of platelet function suppressive drugs, such a non-steroidal anti-inflammatory drugs (NSAIDs), was discouraged but not prohibited by the protocol. (n=64) Intervention 2: Vitamin K antagonists - Warfarin (all doses). 5.0mg beginning the night before surgery, followed by 5.0mg the PM of surgery, and then variable daily dose (target INR 2.0-2.5). All patients wore pneumatic compression stockings while in-patient. AES were prescribed to be used after discharge until the follow-up ultrasounds. Duration 28±2 days. Concurrent medication/care: Use of platelet function suppressive drugs, such a non-steroidal anti-inflammatory drugs (NSAIDs), was discouraged but not prohibited by the protocol.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX + IPCD + AES versus WARFARIN + IPCD + AES	

Study	Bern 2015[28]
Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 28±2 days; Group 1: 0/54, Group 2: 0/64 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 28±2 days; Group 1: 0/54, Group 2: 0/64 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 28±2 days; Group 1: 0/54, Group 2: 0/64 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 28±2 days; Group 1: 0/54, Group 2: 0/64 Protocol outcome 5: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 28±2 days; Group 1: 0/54, Group 2: 0/64	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Blanchard et al., 1999 [31]	RCT	1+	Total: 130 Intervention: 63 Control: 67	Type of surgery: elective knee replacement. Intervention M/F: 11/52 Mean age: 72 Control M/F: 20/47 Mean age: 74	Intermittent pneumatic plantar compression (AVIS (Novomedix)) Started 12 hours preoperatively, discontinued for surgery, reapplied after surgery. Used at all times except during walking and physiotherapy Additional prophylaxis: none	LMWH (calcium nadroparin) injected subcutaneously 12 hours preoperatively the 12 hours postoperatively then once per day for 12 days. Doses adjusted to patient's body weight. Additional prophylaxis: none	2 to 3 months Diagnostic tests carried out 8 to 10 days after surgery. After screening for DVT, all patients received aceno-coumarol for 6 to 8 weeks.	DVT confirmed by phlebography or venous compression US	Int: 34/63 Cont: 16/.67 p value: <0.01	At 2 to 3 month follow up no patients had symptomatic DVT or PE and none died. Also reported Median intraoperative and postoperative blood loss, total blood transfused.
								Proximal DVT confirmed by phlebography or venous compression US	Int: 4/63 Cont: 2/.67 p value: 0.4	
								Distal DVT confirmed by phlebography or venous compression US	Int: 30/63 Cont: 14/.67 p value: <0.005	
								Symptomatic PE	Int: 0/63 Cont: 0/.67 p value: N/A	
								Major bleeds	Int: 0/63 Cont: 1/67 p value: not significant	

Study	Chin 2009[49]
Study type	RCT (Patient randomised; Parallel)

Study	Chin 2009[49]
Number of studies (number of participants)	N/A (n=n=440)
Countries and setting	Conducted in Singapore; Setting: Hospital during intervention and post-discharge follow-up.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 5 to 7 days of intervention + Up to 1 month of follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnostic criteria: loss of compressibility of a vein or visualisation of thrombosis. Investigations performed: ventilation-perfusion scanning; spiral computed tomography of the chest; duplex ultrasonography.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Low risk patients with no predisposition to thromboembolism who underwent elective TKA.
Exclusion criteria	Use of anticoagulants/aspirin; history of PE/DVT in previous year; obesity (BMI>30); pre-operative prolonged immobilisation or being wheelchair-bound; bleeding tendency or history of GI bleeding; surgery in previous 6 months; cerebrovascular accident in previous 3 months; uncontrolled hypertension; congestive cardiac failure; renal/liver impairment; allergy to heparin / heparin-induced thrombocytopenia; varicose veins / chronic venous insufficiency; peripheral vascular disease; skin ulcers; dermatitis/wounds; malignancy.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): Control 65 (47-77); AES 67 (51-81); Intermittent pneumatic compression 65 (49-85); Enoxaparin 67 (52-78). Gender (M:F): 43:397. Ethnicity: Chinese n=403 (91.6%); Malay n=16 (3.6%); Indian n=21 (4.8%)
Further population details	1. BMI : 2. Renal impairment:
Extra comments	.
Indirectness of population	Serious indirectness: The composition of ethnic groups is different to that of the UK population. Incidence and prevalence of VTE are significantly lower in Asian populations than in other ethnic groups.
Interventions	(n=110) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 40mg once daily. Duration 5 to 7 days (stopped earlier if DVT/PE suspected). Concurrent medication/care: Standardised rehabilitation: continuous passive movements on day 2 then ambulation on day 3 (n=110) Intervention 2: Intermittent pneumatic compression devices - Full leg. One minute per inflation-deflation cycle and pressures from 45 to 52mmHg. Duration 5 to 7 days (stopped earlier if DVT/PE suspected). Concurrent medication/care: Standardised rehabilitation: continuous passive movements on day 2 then ambulation on day 3 Comments: Unknown whether the pressure was applied to below knees only or full legs.

Study	Chin 2009[49]
	(n=110) Intervention 3: Anti-embolism stockings - Mixed above/below knee. Applied directly to both legs. Duration 5 to 7 days (stopped earlier if DVT/PE suspected). Concurrent medication/care: Standardised rehabilitation: continuous passive movements on day 2 then ambulation on day 3 Comments: Stocking length unknown (n=110) Intervention 4: No treatment - Usual care. No prophylaxis. Duration N/A. Concurrent medication/care: Standardised rehabilitation: continuous passive movements on day 2 then ambulation on day 3
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (40MG ONCE DAILY) versus INTERMITTENT PNEUMATIC COMPRESSION (IPC)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: Overall prevalence of DVT at Up to 1 month post-surgery; Group 1: 6/110, Group 2: 9/110
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 0/110
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at time-point not reported; Group 1: 2/110, Group 2: 0/110
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Technical complications of mechanical interventions at duration of study
- Actual outcome: Technical complications of mechanical interventions at time-point not reported; Group 1: 0/110, Group 2: 0/110

Study	Chin 2009[49]
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Infection at duration of study - Actual outcome: Number of participants re-admitted due to superficial wound infections at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 1/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: Distal DVT at Up to 1 month post-surgery; Group 1: 5/110, Group 2: 9/110 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Proximal DVT at Up to 1 month post-surgery; Group 1: 1/110, Group 2: 0/110 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (40MG ONCE DAILY) versus AES Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: Overall prevalence of DVT at Up to 1 month post-surgery; Group 1: 6/110, Group 2: 14/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 1/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at time-point not reported; Group 1: 2/110, Group 2: 0/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0	

Study	Chin 2009[49]
Protocol outcome 4: Technical complications of mechanical interventions at duration of study - Actual outcome: Technical complications of mechanical interventions at time-point not reported; Group 1: 0/110, Group 2: 0/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Infection at duration of study - Actual outcome: Number of participants re-admitted due to superficial wound infections at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 2/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: Distal DVT at Up to 1 month post-surgery; Group 1: 5/110, Group 2: 13/110 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Proximal DVT at Up to 1 month post-surgery; Group 1: 1/110, Group 2: 3/110 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (40MG ONCE DAILY) versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: Overall prevalence of DVT at Up to 1 month post-surgery; Group 1: 6/110, Group 2: 24/110; Comments: p = 0.001 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 1/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at time-point not reported; Group 1: 2/110, Group 2: 0/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;	

Study	Chin 2009[49]
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Technical complications of mechanical interventions at duration of study - Actual outcome: Technical complications of mechanical interventions at time-point not reported; Group 1: 0/110, Group 2: 0/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Infection at duration of study - Actual outcome: Number of participants re-admitted due to superficial wound infections at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 2/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: Distal DVT at Up to 1 month post-surgery; Group 1: 5/110, Group 2: 21/110 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Proximal DVT at Up to 1 month post-surgery; Group 1: 1/110, Group 2: 3/110 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERMITTENT PNEUMATIC COMPRESSION (IPC) versus AES Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: Overall prevalence of DVT at Up to 1 month post-surgery; Group 1: 9/110, Group 2: 14/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 1/110 Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at time-point not reported; Group 1: 0/110, Group 2: 0/110	

Study	Chin 2009[49]
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Technical complications of mechanical interventions at duration of study - Actual outcome: Technical complications of mechanical interventions at time-point not reported; Group 1: 0/110, Group 2: 0/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Infection at duration of study - Actual outcome: Number of participants re-admitted due to superficial wound infections at Up to 1 month post-surgery; Group 1: 1/110, Group 2: 2/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: Distal DVT at Up to 1 month post-surgery; Group 1: 9/110, Group 2: 13/110 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Proximal DVT at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 1/110 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERMITTENT PNEUMATIC COMPRESSION (IPC) versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: Overall prevalence of DVT at Up to 1 month post-surgery; Group 1: 9/110, Group 2: 24/110; Comments: p = 0.032 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 1/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening	

Study	Chin 2009[49]
clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at time-point not reported; Group 1: 0/110, Group 2: 0/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Technical complications of mechanical interventions at duration of study - Actual outcome: Technical complications of mechanical interventions at time-point not reported; Group 1: 0/110, Group 2: 0/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Infection at duration of study - Actual outcome: Number of participants re-admitted due to superficial wound infections at Up to 1 month post-surgery; Group 1: 1/110, Group 2: 2/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: Distal DVT at Up to 1 month post-surgery; Group 1: 9/110, Group 2: 21/110 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Proximal DVT at Up to 1 month post-surgery; Group 1: 0/110, Group 2: 3/110 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AES versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: Overall prevalence of DVT at Up to 1 month post-surgery; Group 1: 14/110, Group 2: 24/110; Comments: p = 0.119 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Up to 1 month post-surgery; Group 1: 1/110, Group 2: 1/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	

Study	Chin 2009[49]
Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at time-point not reported; Group 1: 0/110, Group 2: 0/110 Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 4: Technical complications of mechanical interventions at duration of study - Actual outcome: Technical complications of mechanical interventions at time-point not reported; Group 1: 0/110, Group 2: 0/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Infection at duration of study - Actual outcome: Number of participants re-admitted due to superficial wound infections at Up to 1 month post-surgery; Group 1: 2/110, Group 2: 2/110 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: Distal DVT at Up to 1 month post-surgery; Group 1: 13/110, Group 2: 21/110 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Proximal DVT at Up to 1 month post-surgery; Group 1: 1/110, Group 2: 3/110	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study;

Study	Cho 2013[51]
Study type	RCT (Patient randomised; Parallel)

Study	Cho 2013[51]
Number of studies (number of participants)	N/A (n=148)
Countries and setting	Conducted in South Korea; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 5 to 7 days of intervention + 90-day follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Assessment of clinical symptoms, Doppler ultrasonography, ventilation perfusion lung scan, CT pulmonary angiography
Stratum	Overall:
Subgroup analysis within study	Not applicable
Inclusion criteria	All adult patients with a diagnosis of primary osteoarthritis of the knee and undergoing elective unilateral primary TKA.
Exclusion criteria	Patients undergoing bilateral knee replacements, preoperative diagnosis of chronic or acute DVT, active bleeding, documented congenital/acquired bleeding disorders, current ulcerative/angiodysplastic GI disease, haemorrhagic stroke or brain/spinal/ophthalmologic surgery in previous 3 months, contraindication to anticoagulant therapy, serum creatinine concentration above 2mg/dl in a well-hydrated patient, platelet count below 100,000/m^3.
Recruitment/selection of patients	From November 2008 to October 2011 patients undergoing elective primary TKA were recruited.
Age, gender and ethnicity	Age - Mean (SD): Intervention 68.5 (6.0) vs. Placebo 68.5 (5.5). Gender (M:F): 12:136. Ethnicity: East Asian
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI in both groups 27.1 kg/m2). 2. Renal impairment: Not applicable
Extra comments	.
Indirectness of population	Serious indirectness: The study participants are East Asians. Incidence and prevalence of VTE are significantly lower in Asian populations than in other ethnic groups.
Interventions	(n=74) Intervention 1: Fondaparinux - Fondaparinux (all doses). Subcutaneous injection of 2.5mg first at 6 to 8 hrs after the surgery, then the second 24hrs after the first. Daily single dose continued until day 5. Duration 5 days. Concurrent medication/care: AES and the same rehabilitation protocol were applied in all patients. Patient-controlled analgesia using IV fentanyl was used until day 2 post-operation. (n=74) Intervention 2: No treatment - Placebo. Isotonic saline injection 0.25ml once daily. First at 6 to 8 hrs after the surgery, then the second at 24hrs after the first one. Daily single dose continued until day 5. Duration 5 days. Concurrent medication/care: As per the fondaparinux group.
Funding	Funding not stated

Study	Cho 2013[51]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX 2.5MG versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Deaths at 90 days post-surgery; Group 1: 0/74, Group 2: 0/74
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: Prevalence of total DVT at 7 days post-surgery; Group 1: 5/74, Group 2: 19/74
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Symptomatic PE at 7 days post-surgery; Group 1: 0/74, Group 2: 0/74
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Incidence of major bleeding at 90 days post-surgery; Group 1: 0/74, Group 2: 0/74
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: VTE at 7-90 days from hospital discharge
- Actual outcome: Prevalence of VTE at Between day 7 and day 90 post-surgery; Group 1: 0/74, Group 2: 0/74

Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge
- Actual outcome: Distal DVT at 7 days; Group 1: 4/74, Group 2: 15/74

Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge
- Actual outcome: Proximal DVT at 7 days; Group 1: 1/74, Group 2: 4/74

Study	Cho 2013[51]
Protocol outcome 8: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at 90 days post-surgery; Group 1: 0/74, Group 2: 0/74	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Colwell 1995[69]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=453)
Countries and setting	Conducted in USA; Setting: Multicentre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 15 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and premenopausal (if documented to be not pregnant) or post menopausal females patients 40 years of age or older
Exclusion criteria	Failure to achieve postoperative hemostasis; documented history or positive clinical evidence of DVT; history of generalised haemorrhagic disorders or any clinically significant diseases that might interfere with the study medications; documented allergy to UFH, fish, swine products or radiopaque dye; uncontrolled asthma, history of heparin associated thrombocytopenia or skin rash; current evidence of drug or alcohol abuse; active ulcerative disease or gastrointestinal haemorrhage within the past 6 months; uncontrolled hypertension; surgery on the eye, spinal cord, or central nervous system within 3 months; scheduled simultaneous multiple joint replacements; documented cerebral vascular accident within 3 months; treatment with other investigational therapeutic agents

Study	Colwell 1995[69]
	within 4 weeks; or treatment with aspirin or NSAID drugs on a regular basis for 4 days preceding hospitalisation.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 68.0 (9.2). Gender (M:F): 1:1.3. Ethnicity: White 92.5%, Black 5.3%, Asian 0.2%, Hispanic 1.5%, other 2%
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=228) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 30mg every 12 hours. Study medication began on the day of surgery within 8 hours of surgical closure after adequate hemostasis. The medication was continued for a minimum of 4 days and as long as 14 days. Duration 4-14 days. Concurrent medication/care: Not reported (n=225) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH 5000U every 8 hours. Study medication began on the day of surgery within 8 hours of surgical closure after adequate hemostasis. The medication was continued for a minimum of 4 days and as long as 14 days. Duration 4-14 days. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asypmtomatic) at 15 days; Group 1: 56/145, Group 2: 77/143
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 83; Group 2 Number missing: 82

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 15 days; Group 1: 0/145, Group 2: 1/143
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 83; Group 2 Number missing: 82

Study	Colwell 1995[69]
Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 15 days; Group 1: 3/228, Group 2: 3/225 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: VTE at 7-90 days from hospital discharge - Actual outcome: VTE at 15 days; Group 1: 56/228, Group 2: 77/225 Protocol outcome 5: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 15 days; Group 1: 51/145, Group 2: 54/143 Protocol outcome 6: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 15 days; Group 1: 5/145, Group 2: 22/143 Protocol outcome 7: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Operative site bleeding at 15 days; Group 1: 9/228, Group 2: 5/225	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Comp 2001[71]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=438)
Countries and setting	Conducted in USA; Setting: Multicentre trial

Study	Comp 2001[71]
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 29 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing elective knee replacement who gave written consent
Exclusion criteria	Patients undergoing multiple joint replacement or in whom hemostasis was not achieved within 12-24 hours after surgery. Patients treated with knee replacement who had undergone surgery on the ipsilateral hip, the contralateral hip or contralateral knee within the previous three months. Clinical evidence of chronic or acute DVT; a history of venous thromboembolic disease within 12 months before the surgery; generalised haemorrhagic diathesis or hypercoagulable syndrome; a documented allergy to UFH or a history of heparin associated thrombocytopenia; a skin rash or necrosis; allergy to fish or swine products, iodine, or radiopaque contrast medium; current drug or alcohol abuse; surgery on the eye, spinal cord or central nervous system; documented stroke or myocardial infarction within one month before entry into the study; active ulcerative disease or angiodysplasia of the gastrointestinal tract; active gastrointestinal bleeding within the last 6 months; uncontrolled hypertensin; use of aspirin-containing products or NSAID agents daily within the four days preceding hospitalisation; receipt of another investigational drug within the preceding 4 weeks; and clinically relevant diseases or treatments that could interfere with the study medications or their evaluation.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): LMWH group, 66.2 (39-87); placebo group, 66.3 (34-88). Gender (M:F): 1:1.34. Ethnicity: Not reported
Further population details	1. BMI : Obese (BMI over 30 kg/m2) (Mean BMI LMWH group = 31.4 (19.8-51.8); placebo group = 31.1 (17.2-55.7)). 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=217) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin, high dose, extended duration (30mg twice daily). Enoxaparin treatment was initiated 12-24 hours postoperatively and continued for 7-10 days. Patients were then administered 40mg once daily subcutaneously for 3 weeks. Duration 28-31 days. Concurrent medication/care: Not reported (n=221) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin, high dose, standard duration (30mg twice daily). Enoxaparin treatment was initiated 12-24 hours

Study	Comp 2001[71]
	postoperatively and continued for 7-10 days. Patients were then administered saline soluation once daily subcutaneously for 3 weeks. Duration 28-31 days. Concurrent medication/care: Not reported
Funding	Study funded by industry (Funds were received in total or partial support of the research from Aventis Pharmaceuticals Incorporated, Bridgewater, New Jersey and Aventis Pharma SA Antony, France)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) EXTENDED DURATION versus ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) STANDARD DURATION

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 27-29 days; Group 1: 33/155, Group 2: 37/144
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 62; Group 2 Number missing: 77

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 27-29 days; Group 1: 0/217, Group 2: 2/221
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 27-29 days; Group 1: 0/217, Group 2: 1/221
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge
- Actual outcome: Clinically relevant non-major bleeding (hemorrhage) at 27-29 days; Group 1: 5/217, Group 2: 8/221
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Comp 2001[71]
Protocol outcome 5: Heparin-induced thrombocytopenia at duration of study - Actual outcome: Thrombocytopenia at 27-29 days; Group 1: 2/217, Group 2: 2/221 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 27-29 days; Group 1: 25/155, Group 2: 26/144 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 27-29 days; Group 1: 8/155, Group 2: 11/144 Protocol outcome 8: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at 27-29 days; Group 1: 0/217, Group 2: 0/221	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	RE-MODEL trial: Eriksson 2007[96]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1393)
Countries and setting	Conducted in Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Poland, South Africa, Spain, Sweden; Setting: 105 centers in Europe, Australia and South Africa
Line of therapy	Not applicable
Duration of study	Intervention time: 6-10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of DVT was established as a consistent intraluminal filling defect on at least two venogram images. PE was established by ventilation/perfusion scintigraphy, pulmonary angiography, spiral computed tomography, or autopsy. Major bleeding defined as fatal bleeding; clinically overt bleeding associated with a decrease in the haemoglobin level

Study	RE-MODEL trial: Eriksson 2007[96]
	of more than 20 g/l compared with the pre-randomisation level; clinically overt bleeding leading to transfusion of two or more units of whole blood or packed cells; critical bleeding (intracerebral, intraocular, intraspinal, pericardial or retroperitoneal); bleeding warranting treatment cessation; bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (e.g. draining or puncture of an haematoma at the surgical site, transfer to an ICU or emergency room) Clinically relevant non-major bleeding defined as any clinically overt bleeding that does not meet the criteria for major bleed but requires medical attention (e.g.: hospitalisation, medical treatment for bleeding) and/or a change in antithrombotic therapy (including discontinuation or down- titration of study drug) and/or any other bleeding type considered to have clinical consequences for a patient.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients ≥18 years and >40 kg, scheduled for primary elective unilateral total knee replacement who provided signed informed consent, were eligible for study
Exclusion criteria	Exclusion criteria included: any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the past 3 months; gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; aspartate aminotransferase or alanine aminotransferase (ALT) levels more than two times the upper limit of the normal range (ULN) within the past month; severe renal insufficiency (creatinine clearance <30 mL min−1); concomitant long-acting non-steroidal anti-inflammatory drug therapy (also contraindicated during study treatment); active malignant disease; and being female and of childbearing potential.
Recruitment/selection of patients	Patients enrolled between November 2004 and March 2006
Age, gender and ethnicity	Age - Mean (SD): 68 (9) years. Gender (M:F): 1/2. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Extra comments	Mean duration of surgery: 90.5 minutes
Indirectness of population	No indirectness
Interventions	(n=699) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Patients were assigned to oral dabigatran etexilate enoxaparin (Sanofi-Aventis), 40 mg subcutaneously once-daily. All three groups received one active and one matching placebo treatment that were identical in appearance. Patients received two capsules in the morning and a daily subcutaneous injection in the evening. The first subcutaneous injection was given on the evening before surgery, although in some countries treatment was started postoperatively to reflect local practice. The first dose of dabigatran etexilate was one-half of subsequent doses (one

Study	RE-MODEL trial: Eriksson 2007[96]
	capsule), and was administered 1–4 h after completion of surgery, provided that clinical assessment of perioperative and postoperative bleeding and drainage indicated good hemostasis. If administration was delayed until the day after surgery, then a full dose (two capsules) was administered as the first dose. Duration 6-10 days. Concurrent medication/care: Concomitant treatment with low-dose aspirin (<160 mg) and selective cycloxygenase-2 inhibitors was allowed during the treatment period. AES were permitted (percentage of patients that wore AES not reported), but intermittent pneumatic compression devices were prohibited. (n=694) Intervention 2: Dabigatran - Dabigatran (all doses). Patients were assigned to oral dabigatran etexilate 220 mg once-daily. All three groups received one active and one matching placebo treatment that were identical in appearance. Patients received two capsules in the morning and a daily subcutaneous injection in the evening. The first subcutaneous injection was given on the evening before surgery, although in some countries treatment was started postoperatively to reflect local practice. The first dose of dabigatran etexilate was one-half of subsequent doses (one capsule, 75 mg or 110 mg), and was administered 1–4 h after completion of surgery, provided that clinical assessment of perioperative and postoperative bleeding and drainage indicated good hemostasis. If administration was delayed until the day after surgery, then a full dose (two capsules) was administered as the first dose. Duration 6-10 days. Concurrent medication/care: Concomitant treatment with low-dose aspirin (<160 mg) and selective cycloxygenase-2 inhibitors was allowed during the treatment period. AES were permitted (percentage of patients that wore AES not reported), but intermittent pneumatic compression devices were prohibited.
Funding	Study funded by industry (Boehringer Ingelheim, Copenhagen, Denmark)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (40MG) versus DABIGATRAN (ALL DOSES)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 13 days; Group 1: 1/685, Group 2: 1/675
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14; Group 2 Number missing: 19

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 13 days; Group 1: 192/685, Group 2: 182/675
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 188, Reason: Venography not performed; venography inadequate; Group 2 Number missing: 191, Reason: Venography not performed; venography inadequate

Study	RE-MODEL trial: Eriksson 2007[96]

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 13 days; Group 1: 1/685, Group 2: 0/675
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: Venography not performed; venography inadequate; Group 2 Number missing: 19, Reason: Venography not performed; venography inadequate

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 13 days; Group 1: 9/694, Group 2: 10/679
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Venography not performed; venography inadequate; Group 2 Number missing: 15, Reason: Venography not performed; venography inadequate

Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 13 days; Group 1: 1/685, Group 2: 0/675
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: Venography not performed; venography inadequate; Group 2 Number missing: 19, Reason: Venography not performed; venography inadequate

Protocol outcome 6: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge
- Actual outcome: Clinically relevant non-major bleeding at 13 days; Group 1: 37/694, Group 2: 40/679
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Venography not performed; venography inadequate; Group 2 Number missing: 15, Reason: Venography not performed; venography inadequate

Protocol outcome 7: VTE at 7-90 days from hospital discharge
- Actual outcome: VTE ([symptomatic or venographic deep vein thrombosis (DVT) and/or symptomatic pulmonary embolism (PE)], and all-cause mortality) at 13 days; Group 1: 193/512, Group 2: 183/503

Protocol outcome 8: DVT (symptomatic) at 7-90 days from hospital discharge

Study	RE-MODEL trial: Eriksson 2007[96]
- Actual outcome: DVT (symptomatic) at 6-10 days; Group 1: 8/685, Group 2: 1/675 Protocol outcome 9: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: Asymptomatic DVT (distal) at 6-10 days; Group 1: 168/685, Group 2: 168/675 Protocol outcome 10: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Asymptomatic DVT (proximal) at 6-10 days; Group 1: 16/685, Group 2: 13/675 Protocol outcome 11: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at 13 days; Group 1: 0/694, Group 2: 0/679 Protocol outcome 12: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Surgical site at 13 days; Group 1: 9/694, Group 2: 10/679	
Protocol outcomes not reported by the study	Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study

Study	Faunø 1994[101]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=185)
Countries and setting	Conducted in Denmark, Finland; Setting: Multicentre trial in three hospitals in Finland and Denmark
Line of therapy	Not applicable
Duration of study	Intervention time: 7-10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	More than 40 years old, scheduled to have a primary unilateral knee replacement and diagnosed as having osteoarthrosis or rheumatoid arthritis.
Exclusion criteria	Managed with anticoagulants; had received platelet aggregation inhibitors, salicylates, or non-steroidal anti-

Study	Faunø 1994[101]
	inflammatory drugs within seven days before the operation; had a history of bleeding disorder; had abnormal preoperative coagulation values, including a platelet count of less than 80x10^9 per litre or a prothrombin time outside the range of 80 to 120 percent of normal; had indications of internal bleeding; had untreated hypertension; had a hypersensitivity to heparins or contrast media; or had had a previous DVT or PE
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 71 (11); UFH group 70 (10). Gender (M:F): 1:1.5. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=92) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin, standard dose (40mg once daily) + AES. The first dose was given the evening before the operation, and continued for 7-10 days. All patients wore a short AES on the involved limb and a long AES on the contralateral limb. Duration 7-10 days. Concurrent medication/care: Not reported (n=93) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH (5000U), three times daily + AES. The first dose was given the evening before the operation, and continued for 7-10 days. All patients wore a short AES on the involved limb and a long AES on the contralateral limb. Duration 7-10 days. Concurrent medication/care: Not reported
Funding	Study funded by industry (Funds were received in total or partial support by Rhone-Poulenc Rorer, Helsinki, Finland, and Birkerod, Denmark)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 7-10 days; Group 1: 21/92, Group 2: 25/93
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 7-10 days; Group 1: 0/92, Group 2: 0/93

Study	Faunø 1994[101]
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Wound haematoma at 7-10 days; Group 1: 8/92, Group 2: 12/93 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Infection at duration of study - Actual outcome: Wound infection at 7-10 days; Group 1: 1/92, Group 2: 3/93 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 7-10 days; Group 1: 18/92, Group 2: 20/93 Protocol outcome 6: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 7-10 days; Group 1: 3/92, Group 2: 5/93	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Fitzgerald 2001[103]
Study type	RCT (Patient randomised; Parallel)

Study	Fitzgerald 2001[103]
Number of studies (number of participants)	1 (n=349)
Countries and setting	Conducted in USA; Setting: Multicentre
Line of therapy	Not applicable
Duration of study	Intervention time: 4-14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women, 38 years of age or older, undergoing a primary unilateral knee arthroplasty
Exclusion criteria	Wound haemorrhage continuing for longer than 8 hours after wound closure, generalised haemorrhagic disorders or hypercoagulable syndrome, including clinical evidence of chronic or acute DVT or a documented history of VTE; allergy to UFH, warfarin, fish or swine products, iodine or contrast medium; a history of heparin associated thrombocytopenia or heparin or warfarin associated skin rash or necrosis; asthma not under medical control; surgery (other than knee arthroplasty); on the ipsilateral knee within the previous 6 months or on the ipsilateral hip, contralateral hip or contralateral knee within the preceding 3 months; any clinically importance disease or requirement for treatment during the study period that could interfere with the action, kinetics or evaluation of the study medications; hepatic disease with a bilirubin level of 2mg/dL; renal disease with a creatinine level of >2mg/dL; evidence of current abuse of drugs (excluding tobacco products) or alcohol; surgery involving the eye, spinal cord or central nervous system within 3 months before study entry; active ulcerative disease or angiodysplasia of the gastrointestinal tract or active gastrointestinal haemorrhage within the previous 6 months; hypertension not under medical control; stroke or myocardial infarction within the previous 3 months; and treatment with aspirin, aspirin containing products, or non-steroidal anti-inflammatory drugs on a regular basis for the four days immediately preceding hospitalisation or regular treatment with these products during hospitalisation.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 38-89. Gender (M:F): 153:196. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=173) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin, high dose (30mg twice daily), administered on the day of surgery, within eight hours of wound closure. The treatment drug was administered for a minimum of 4 days and a maximum of 14 days. Duration 4-14 days. Concurrent medication/care: Sequential compression devices were not permitted, but AES were. Use of continuous passive motion device was permitted for a total of 6 hours per day

Study	Fitzgerald 2001[103]
	(n=176) Intervention 2: Vitamin K antagonists - Warfarin (all doses). Warfarin was initiated orally with a dose of 7.5mg, followed by subsequent daily adjustment of the dose as necessary to maintain the INR between 2-3. The treatment drug was administered for a minimum of 4 days and a maximum of 14 days. Duration 4-14 days. Concurrent medication/care: Sequential compression devices were not permitted, but AES were. Use of continuous passive motion device was permitted for a total of 6 hours per day
Funding	Study funded by industry (Funds were received in total or partial support, from Aventis Pharmaceuticals, Incorporated, Bridgewater, New Jersey)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus WARFARIN (ALL DOSES)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 15 days; Group 1: 1/173, Group 2: 3/176
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 15 days; Group 1: 44/173, Group 2: 79/176
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 15 days; Group 1: 0/173, Group 2: 1/176
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 15 days; Group 1: 9/173, Group 2: 4/176
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Study	Fitzgerald 2001[103]
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding at 15 days; Group 1: 12/173, Group 2: 6/176 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Wound haematoma at 15 days; Group 1: 3/173, Group 2: 0/176 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 15 days; Group 1: 41/173, Group 2: 59/176 Protocol outcome 8: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 15 days; Group 1: 3/173, Group 2: 20/176 Protocol outcome 9: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at 15 days; Group 1: 0/173, Group 2: 1/176	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fuji et al., 2008[112]	Patient group: Study 1: Total knee replacement (TKR) Study 2: Total hip replacement	Study 1 (TKR) Group 1 LMWH	Symptomatic pulmonary Embolism (description: ventilation perfusion lung scans or	Study 1 (TKR) Group 1: 1/78 Group 2: 1/74	Funding: Sanofi-Aventis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: Japan Study design: RCT List who was masked to interventions: Paper states that study is double blind (see limitations) and that the endpoint assessors were blinded. Evidence level: 1+ Duration of follow-up: 90 days	(THR) Setting: Department of Orthopaedic Surgery Inclusion criteria: Patients aged ≥ 20 years (no upper age limit was applied) undergoing elective primary THR or TKR. Exclusion criteria: ■ Patients requiring revision TKR or revision THR Contraindication to heparin therapy Positive clinical evidence of chronic (post-phlebitic syndrome) or acute DVT within 12 months of the study drug treatment ■ Documented allergy to iodine or contrast medium ■ impaired renal function (creatinine clearance <30ml/min or plasma creatinine level >1.5mg/dl) Severe hepatic disease Uncontrolled hypertension Illicit drug use or alcohol abuse Treatment with other investigational agents within 3 months of surgery ■ Failure to achieve postoperative haemostasis	(Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 20mg subcutaneous injection Group 2 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 40 mg subcutaneous injection Group 3 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Twice daily 20mg subcutaneous injections Group 4	pulmonary angiography at 90 days)	Group 3: 0/84 Group 4: 1/79 p value: Not significant Study 2 (THR) Group 5: 0/81 Group 6: 1/80 Group 7: 0/90 Group 8: 0/86 p value: Not significant	Limitations: Method of randomisation not given. No details provided on allocation concealment. Study reports that it was blinded but no information provided and some of the injection regimens were once daily whilst others were twice daily. Outcomes not reported: All-cause mortality, fatal bleeding, fatal PE, heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay Additional outcomes reported: The total number of
			DVT, asymptomatic or symptomatic (screened for by: Doppler ultrasound at 14 days)	Study 1 (TKR) Group 1: 34/78 Group 2: 26/74 Group 3: 25/84 Group 4: 48/79 p value: All groups receiving LMWH (gp 1,2 & 3) had significantly less DVT than the placebo group (gp 4). Group 1 vs. Group 4 = 0.038* Group 2 vs. Group 4 = 0.002* Group 3 vs. Group 4 = <0.001* No other significant differences between groups were found. Study 2 (THR) Group 5: 21/81 Group 6: 27/80 Group 7: 18/90	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	[redacted] Female subjects if pregnant or breast- feeding. Study 1 (TKR) All patients N: 396 No. of dropouts: 32 (8.1%) Group 1 No. analysed: 78 Age (mean): 68.8 (sd = 9.0) M/F: 15:63 Additional risk factors: BMI ≥ 25 kg/m2 = 40 (51.3%) Group 2 No. analysed: 74 Age (mean): 70.0 (sd = 9.4) M/F: 11:63 Additional risk factors: BMI ≥ 25 kg/m2 = 44 (59.4%) Group 3 No. analysed: 84 Age (mean): 68.3 (sd = 8.7) M/F: 5:79 Additional risk factors: BMI ≥ 25 kg/m2 = 35 (41.7%) Group 4 No. analysed: 79 Age (mean): 68.7 (sd =9.5)	Placebo (saline) Start time: 24-36 hrs after surgery Duration: 14 days Subcutaneous injections (no frequency stated) Additional non-comparative prophylaxis: More than 50% of patients received elastic stockings /bandages for part of the study. No other prophylaxis was used. Study 2 (THR) Group 5 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 20mg subcutaneous injections		Group 8: 36/86 p value: The group receiving twice daily injections of 20mg LMWH (gp 7) had significantly less DVT than the placebo group (gp 8) p = 0.003* No other significant differences between groups were found	adverse events were recorded. The authors concluded that most of these were not related to the treatment under investigation. Notes: * calculated by NCC using fishers exact test.
			Thigh DVT (description: screened for by: Doppler ultrasound at 14 days)	Study 1 (TKR) Group 1: 6/78 Group 2: 3/74 Group 3: 0/84 Group 4: 6/79 p value: There were significantly fewer events in the twice daily 20mg LMWH group (gp3) vs the once daily 20mg LMWH group (gp 1) (p = 0.011*). There were significantly fewer events in the twice daily 20mg LMWh group (gp3) vs. the placebo group (gp 4) (p = 0.012*) Study 2 (THR) Group 5: 3/81 Group 6: 6/80 Group 7: 3/90	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 15: 64 Additional risk factors: BMI ≥ 25 kg/m2 = 40 (50.6%) Study 2 (THR) All patients N: 436 No. of dropouts: 29 (6.7%) Group 5 No. analysed: 81 Age (mean): 63.3 (sd = 10.4) M/F: 10: 71 Additional risk factors: BMI ≥ 25 kg/m2 = 23 (28.4%) Group 6 No. analysed: 80 Age (mean): 60.6 (sd = 9.9) M/F: 6:74 Additional risk factors: BMI ≥ 25 kg/m2 = 26 (35.2%) Group 7 No. analysed: 90 Age (mean): 63.0 (sd = 9.3) M/F: 15:75 Additional risk factors: BMI ≥ 25 kg/m2 = 31 (34.4%) Group 8	Group 6 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 40 mg subcutaneous injections Group 7 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Twice daily 20mg subcutaneous injections Group 8 Placebo (saline) Start time: 24-36 hrs after surgery Duration: 14 days Subcutaneous injections (no frequency stated)		Group 8: 9/86 p value: No significant difference	
		Major bleeding (description: bleeding episode that was retroperitoneal, intracranial, or intraocular o if it was associated with: death; transfusion of ≥2 units of packed red blood cells or whole blood (except autologous); a reduction of ≥2 g/d; or a serious or life threatening clinical events that required medical intervention.)	Study 1 (TKR) Group 1: 0/89 Group 2: 1/91 Group 3: 3/95 Group 4: 4/89 p value: Not significant Study 2 (THR) Group 5: 1/100 Group 6: 2/102 Group 7: 3/104 Group 8: 0/101 p value: Not significant	
		Minor bleeding (description: at least one of the following features: epistaxis lasting >5 minutes or requiring intervention; ecchymosis or hematoma with a maximum size of >5 cm; haematuria not associated with urinary catheter trauma; gastrointestinal haemorrhage not related to intubation or a nasogastric tube;	Study 1 (TKR) Group 1: 5/89 Group 2: 6/91 Group 3: 10/95 Group 4: 4/89 p value: Not significant Study 2 (THR) Group 5: 1/100 Group 6: 7/102 Group 7: 4/104 Group 8: 2/101 p value: Not significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. analysed: 86 Age (mean): 62.0 (sd =10.3) M/F: 11: 75 Additional risk factors: BMI ≥ 25 kg/m2 = 34 (39.5%)	Additional non-comparative prophylaxis: More than 50% of patients received elastic stockings /bandages for part of the study. No other prophylaxis was used.	wound haematoma or haemorrhagic wound complications not associated with major haemorrhage; or subconjunctival haemorrhage requiring cessation of medication)		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fuji et al., 2008A [111] Country of study: Japan Study design: RCT	Patient group: Study 1: Total knee replacement (TKR) Study 2: Total hip replacement (THR) Setting: Department of Orthopaedic Surgery	Study 1 (TKR) Group 1 Fondaparinux (Atrixa) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days	All-cause mortality	Study 1 (TKR) Group1: 0/84 Group 2: 0/87 P value: N/A Study 2 (THR) Group3: 0/81 Group 4: 0/82 P value: N/A	Funding: GlaxoSmithKlein, Sanovi-synthelabo and NV Organon Limitations: Method of randomisation not given. No details provided
			Fatal bleeding	Study 1 (TKR) Group1: 0/84 Group 2: 0/87 P value: N/A Study 2 (THR) Group3: 0/81 Group 4: 0/82 P value: N/A	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
List who was masked to interventions: Paper states that study is double blind and that the endpoint assessors were blinded. Evidence level: 1+ Duration of follow-up: 11-17 days	Inclusion criteria: Patients of either gender if their age was 20 years or greater, and they were scheduled for TKR or THR surgery or revision surgery for TKR or THR Exclusion criteria: Active, clinically significant bleeding Bleeding tendency/disorder (e.g. ulcer of the digestive tract etc.) Severe hepatic disorder Hypersensitivity to UFH or LMWH Requirement of an indwelling intrathecal or epidural catheter during the treatment period [redacted] Brain, spine or ophthalmologic surgery within 3 months preceding enrolment Body weight <40kg Severe renal disorder (serum creatinine concentration >2.0mg/dL) Study 1 (TKR) All patients N: 426 No. of dropouts: 29 (6.8%) Age (mean): 71.0 (sd = 8.0) M/F: 75: 351 Additional risk factors: BMI ≥ 30 kg/m2 = 64 (15.0%) Group 1	Daily 2.5mg subcutaneous injections Group 2 Placebo (0.25ml isotonic sodium chloride) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous injections Additional non-comparative prophylaxis: More than 50% of patients received elastic stockings /bandages for part of the study. Study 2 (THR) Group 3 Fondaparinux (Atrixa) Start time: 24hr ± 2 hrs after surgery	Major bleeding (description: fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with a bleeding index of 2 or more.)	Study 1 (TKR) Group1: 1/84 Group 2: 1/87 P value: 1.00* Study 2 (THR) Group3: 2/81 Group 4: 0/82 P value: 0.245*	on allocation concealment. Outcomes not reported: DVT, PE, Heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay Additional outcomes reported: Incidence of combined VTE was recorded Study 1 (TKR) Group 1: 16.2% Group 2: 65.3% P value: <0.05* Study 2 (THR) Group 3: 7.4% Group 4: 33.8%
			Minor bleeding (description: not defined)	Study 1 (TKR) Group1: 2/84 Group 2: 3/87 P value: 1.00* Study 2 (THR) Group3: 4/81 Group 4: 0/82 P value: 0.059*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 84 Group 2 No. randomised: 87 Study 2 (THR) All patients N: 406 No. of dropouts: 25 (6.2%) Age (mean): 61.6 (sd = 10.9) M/F: 73: 333 Additional risk factors: BMI ≥ 30 kg/m2 = 26 (6.4%) Group 3 No. randomised: 81 Group 4 No. randomised: 82	Duration: 10-16 days Daily 2.5mg subcutaneous injections Group 4 Placebo (0.25ml isotonic sodium chloride) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous injections Additional non-comparative prophylaxis: More than 50% of patients received elastic stockings /bandages for part of the study.			P value: <0.05* Notes: * calculated by NCC using fishers exact test. Study was a dose ranging study with separate groups receiving 0.75, 1.5, 2.5 and 3.0mg fondaparinux. Only the group receiving 2.5 mg fondaparinux is analysed here as this is the licensed dose.

Study	Fuji 2010[110]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=253)
Countries and setting	Conducted in Japan; Setting: Multicentre including 38 centres in Japan
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female patients who were at least 20 years old; had a eight of 40kg or higher; primary, unilateral, elective TKA; and provision of signed informed consent
Exclusion criteria	Any bleeding diathesis; major surgery, trauma, uncontrolled hypertension, or myocardial infarction within the last 3 months; clinical relevant bleeding or gastric/duodenal ulcer within the last 6 months; history of haemorrhagic stroke or acute intracranial bleeding; history of VTE or preexisting condition requiring anticoagulant therapy; severe liver disease or elevated aspartate aminotransferase or alanine aminotransferase levels to more than 2 times the upper limit or normal range; significant renal disease; treatment with anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory drugs with t1/2 of more than 12 hours within 7 days before TKA; anticipated requirement for intermittent pneumatic compression of lower limb; pregnancy or women of childbearing potential; history of thrombocytopenia; previous leg amputation; and active malignant disease
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Dabigatran group 72.7 (6.8); Placebo group 71.3 (8.5). Gender (M:F): 1:1.6. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=129) Intervention 1: Dabigatran - Dabigatran (all doses). Oral dabigatran 220mg once daily. The first oral dose was administered as early as possible on the day after surgery or at least 2 hours after removing the indwelling catheter and confirming the absence of abnormal bleeding from the drainage sites. Treatment continued for 11-14 days after surgery.. Duration 11-14 days. Concurrent medication/care: The use of AES and dressings was allowed. IPCD was not permitted. (n=124) Intervention 2: No treatment - Placebo. Placebo, once daily. The first oral dose was administered as early as

Study	Fuji 2010[110]
	possible on the day after surgery or at least 2 hours after removing the indwelling catheter and confirming the absence of abnormal bleeding from the drainage sites. Treatment continued for 11-14 days after surgery. orally given from 'as early as possible' or at least 2 hours after removing the indwelling catheter and confirming the absence of abnormal bleeding from the drainage sites for 11-14 days. Patients received two capsules per day. orally given from 'as early as possible' or at least 2 hours after removing the indwelling catheter and confirming the absence of abnormal bleeding from the drainage sites for 11-14 days. Patients received two capsules per day. Duration 11-14 days. Concurrent medication/care: The use of AES and dressings was allowed. IPCD was not permitted.
Funding	Study funded by industry (Benefits of funds were received in partial or total support from Boehringer Ingelheim Co, Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DABIGATRAN (ALL DOSES) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 14 days; Group 1: 0/129, Group 2: 0/124
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 14 days; Group 1: 23/96, Group 2: 57/101
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 33; Group 2 Number missing: 23

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 14 days; Group 1: 4/129, Group 2: 1/124
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge

Study	Fuji 2010[110]
- Actual outcome: Clinically relevant non-major bleeding at 14 days; Group 1: 2/129, Group 2: 3/124 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Technical complications of mechanical interventions at duration of study - Actual outcome: PE at 14 days; Group 1: 0/129, Group 2: 0/124 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 6: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 14 days; Group 1: 1/129, Group 2: 2/124 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 14 days; Group 1: 0/102, Group 2: 6/104 Protocol outcome 8: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at 14 days; Group 1: 0/129, Group 2: 0/124 Protocol outcome 9: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Critical organ at 14 days; Group 1: 0/129, Group 2: 0/124	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Infection at duration of study;

Study	Ginsberg 2009: RE-MOBILIZE trial: Re-mobilize writing committee 2009[272]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=2615)

Study	Ginsberg 2009: RE-MOBILIZE trial: Re-mobilize writing committee 2009[272]
Countries and setting	Conducted in Multiple countries; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 12 to 15 days + Follow-up 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of DVT was made with bilateral venography. Diagnosis of PE was made with ventilation-perfusion scintigraphy, pulmonary angiography, spiral computed tomography, or autopsy. Symptomatic DVT was confirmed by compression ultrasound or venography.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients older than 18 years and weighing more than 40kg who had undergone primary elective unilateral TKA and provided signed informed consent
Exclusion criteria	Known inherited/acquired clinically significant bleeding disorder; major surgery / trauma / uncontrolled hypertension / MI within last 3 months; history of acute intracranial disease / haemorrhagic stroke; GI/urogenital bleeding / ulcer disease within last 6 months; severe liver disease; aspartate/alanine aminotransferase levels higher than 2x the upper limit of the normal range within last month; severe renal insufficiency; need for concomitant long-acting NSAIDs / treatment with an anticoagulant during study drug treatment; active malignant disease; platelet count < 100 x 10^9/L; pregnancy / nursing / pre-menopausal women of child-bearing potential who were not practising effective birth control; failure to provide informed consent
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Dabigatran 220mg 66.2 ± 9.5 vs. Dabigatran 150mg 65.9 ± 9.5 vs. Enoxaparin 66.3 ± 9.6. Gender (M:F): 1098:1517. Ethnicity: Ethnicity of the participants is not reported. Participants were recruited in the US (58 centres), Canada (30 centres), Mexico (8 centres) and in the UK (1 centre).
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Extra comments	.
Indirectness of population	No indirectness: Incidence and prevalence of VTE vary between different ethnicities. Ethnic composition of the participants is not reported by the study.
Interventions	(n=862) Intervention 1: Dabigatran - Dabigatran (all doses). Oral tablets: first dose of 110mg was given 6 to 12 hrs after surgery then 220mg once daily thereafter. Duration 12 to 15 days. Concurrent medication/care: One additional placebo capsule (dummy) given at the same time as a dabigatran 220mg tablet and a subcutaneous placebo injection to mimic enoxaparin injection (n=877) Intervention 2: Dabigatran - Dabigatran (all doses). Oral tablets: first dose of 75mg was given 6 to 12 hrs after

Study	Ginsberg 2009: RE-MOBILIZE trial: Re-mobilize writing committee 2009[272]
	surgery then 150mg once daily from thereafter. Duration 12 to 15 days. Concurrent medication/care: One additional placebo capsule at the same time as the dabigatran 150mg tablet and a subcutaneous placebo injection to mimic enoxaparin injection (n=876) Intervention 3: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous injection: the first dose of 30mg given 12 to 24 hrs after surgery then the same dose given twice daily from thereafter. Duration 12 to 15 days. Concurrent medication/care: Two placebo tablets given in the morning to match the two dabigatran doses
Funding	Study funded by industry (Boehringer Ingelheim Pharma)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DABIGATRAN 220MG versus ENOXAPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death during treatment period at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1: 1/857, Group 2: 0/868
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported; Group 2 Number missing: 8, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: Total DVT during treatment period at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1: 181/857, Group 2: 248/868
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 253, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported; Group 2 Number missing: 225, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1: 6/604, Group 2: 5/643

Study	Ginsberg 2009: RE-MOBILIZE trial: Re-mobilize writing committee 2009[272]
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 253, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported; Group 2 Number missing: 225, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding during treatment period at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1: 5/857, Group 2: 12/868 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported; Group 2 Number missing: 8, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Death where VTE cannot be ruled out at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1: 1/857, Group 2: 0/868 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported; Group 2 Number missing: 8, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported Protocol outcome 6: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding during treatment period at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1: 23/857, Group 2: 21/868 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported; Group 2 Number missing: 8, Reason: Missing participants were those who were not given a study treatment; reason for not receiving treatment not reported Protocol outcome 7: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1:	

Study	Ginsberg 2009: RE-MOBILIZE trial: Re-mobilize writing committee 2009[272]
167/604, Group 2: 148/643 Protocol outcome 8: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1: 14/604, Group 2: 10/643 Protocol outcome 9: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1: 0/868, Group 2: 0/876 Protocol outcome 10: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Surgical site bleeding at From administration of first dose of study medication to 3 days after administration of last dose of study medication; Group 1: 2/862, Group 2: 11/876	
Protocol outcomes not reported by the study	Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Intiyanaravut 2017[155]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Thailand; Setting: Golden Jubilee Medical Center, Mahidol University, Nakhon Pathom, Thailand
Line of therapy	Not applicable
Duration of study	Intervention time: 7-10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by bilateral colour Doppler ultrasonography PE: confirmed by clinical signs scoring system (sudden dyspnea, chest pain and cough of haemoptysis). Major bleeding: defined as the presence of grade three haematoma which requiring operative removal and bleeding that was fatal or involved a critical organ.
Stratum	Overall

Study	Intiyanaravut 2017[155]
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for elective primary total knee arthroplasty, aged between 50 and 85.
Exclusion criteria	History of DVT or PE, history of haemorrphagic stroke or gastro-intestinal bleeding, renal impairment, the use of anticoagulants, allergy to enoxaparin.
Recruitment/selection of patients	From October 2012 to June 2014
Age, gender and ethnicity	Age - Mean (SD): 71 years. Gender (M:F): 1/4. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI: 28 kg/m2). 2. Renal impairment: Not applicable
Extra comments	Mean length of operation: 130 minutes
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin (40 mg) was subcutaneously administered once daily, starting 24 hours after surgery. Duration 7-10 days. Concurrent medication/care: Postoperative protocol included compressive dressings in the first 24 hours, drain was removed in 48 to 72 hours after operation, continuous passive movement was initiated on second day, followed by active mobilisation and full weight-bearing ambulation. Indirectness: No indirectness (n=25) Intervention 2: No treatment - Usual care. No prophylaxis was given. Duration 7-10 days. Concurrent medication/care: Postoperative protocol included compressive dressings in the first 24 hours, drain was removed in 48 to 72 hours after operation, continuous passive movement was initiated on second day, followed by active mobilisation and full weight-bearing ambulation. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (STANDARD DOSE) versus CONTROL GROUP

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 7-10 days; Group 1: 0/25, Group 2: 1/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect;

Study	Intiyanaravut 2017[155]
autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at time-point not reported; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at time-point not reported; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Lassen 2007[193]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=615)
Countries and setting	Conducted in Multiple countries; Setting: 97 centres in Argentina, Australia, Canada, Mexico, Denmark, Israel, Poland and the USA
Line of therapy	Not applicable
Duration of study	Intervention time: 12 +/- 2 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Lassen 2007[193]
Inclusion criteria	Patients aged 18-90 years, scheduled to have a total knee replacement
Exclusion criteria	Child-bearing potential if a woman; presence of bleeding/coagulation disorders; history of heparin induced thrombocytopenia; intracranial/intraocular heamorrhage within the past 5 years; gastrointestinal bleeding within 90 days of surgery or ulcer disease within 30 days before surgery; brain, spinal, ophthalmologic or major surgery/trauma within 90 days prior to surgery; known VTE disease within the past 12 months; uncontrolled hypertension; malignant disease; active hepatobiliary diease; known or suspected GI disease that may affect absorption of study medication; ALT, AST, or bilirubin (direct or total) >1.5 x upper limit of normal (ULN); INR >1.4 or activated partial thromboplastin time > 1.4 x control value; hypersensitivity to UFH, LMWH, warfarin or other vitamin K antagonists, porcine products or iodinated contrast medium; or treatment with medications affecting coagulation/platelet function within 7 days prior to surgery
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (range): Apixaban 2.5mg bid group 67.6 (46-88); apixaban 5mg qd 66.9 (31-87); LMWH group 66.5 (36-88); VKA group 66.8 (43-85). Gender (M:F): 1:1.7. Ethnicity: Not reported
Further population details	1. BMI : Obese (BMI over 30 kg/m2) (Mean BMI 30.5, 30.6, 30.4 and 30.4 respectively (range 18.3-50.1)). 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=152) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous enoxaparin, high dose (30mg twice daily). Began 12-24 hours after skin wound closure, for a total of 12 +/- 2 days. Duration 12 +/- 2 days. Concurrent medication/care: Not reported (n=310) Intervention 2: Apixaban - Apixaban (all doses). Apixaban 2.5mg twice daily or 5mg once daily given orally. Began 12-24 hours after skin wound closure and continued for 12 +/- 2 days. Duration 12 +/- 2 days. Concurrent medication/care: Not reported (n=153) Intervention 3: Vitamin K antagonists - Warfarin (all doses). Warfarin was administered from the evening of the day of surgery, starting with a dose of 5mg and then continued once a day in the evening for 12 +/- 2 days. Warfarin dose was adjusted to maintain INR in the range of 1.8-3.0. Duration 12 +/- 2 days. Concurrent medication/care: Not reported
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus APIXABAN (ALL DOSES)	

Study	Lassen 2007[193]
	Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 12 +/- 2 days; Group 1: 0/109, Group 2: 1/208 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 43, Reason: 3 not treated, 18 no venography, 22 un evaluable venography; Group 2 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 12 +/- 2 days; Group 1: 15/109, Group 2: 21/208 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 43, Reason: 3 not treated, 18 no venography, 22 un evaluable venography; Group 2 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 12 +/- 2 days; Group 1: 2/109, Group 2: 1/208 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogrpahy Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 12 +/- 2 days; Group 1: 0/149, Group 2: 4/305 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 3, Reason: Not treated; Group 2 Number missing: 5, Reason: Not treated Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 12 +/- 2 days; Group 1: 0/109, Group 2: 1/208 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogrpahy

Study	Lassen 2007[193]

Protocol outcome 6: Infection at duration of study
- Actual outcome: Wound related infections at 12 +/- 2 days; Group 1: 1/149, Group 2: 6/305
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 3, Reason: Not treated; Group 2 Number missing: 5, Reason: Not treated

Protocol outcome 7: VTE at 7-90 days from hospital discharge
- Actual outcome: Total VTE at 12 +/- 2 days; Group 1: 17/109, Group 2: 21/208

Protocol outcome 8: DVT (symptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic) at 12 +/- 2 days; Group 1: 1/109, Group 2: 1/208

Protocol outcome 9: DVT (distal) at 7-90 days from hospital discharge
- Actual outcome: DVT (distal) at 12 +/- 2 days; Group 1: 12/109, Group 2: 18/208

Protocol outcome 10: DVT (proximal) at 7-90 days from hospital discharge
- Actual outcome: DVT (proximal) at 12 +/- 2 days; Group 1: 3/109, Group 2: 3/208

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus WARFARIN (ALL DOSES)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 12 +/- 2 days; Group 1: 0/109, Group 2: 0/109
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 43, Reason: 3 not treated, 18 no venography, 22 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogarpahy

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 12 +/- 2 days; Group 1: 15/109, Group 2: 29/109
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 43, Reason: 3 not treated, 18 no venography, 22 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogarpahy

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect;

Study	Lassen 2007[193]
autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 12 +/- 2 days; Group 1: 2/109, Group 2: 0/109 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogrpahy Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 12 +/- 2 days; Group 1: 0/149, Group 2: 0/151 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 3, Reason: Not treated; Group 2 Number missing: 2, Reason: Not treated Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 12 +/- 2 days; Group 1: 0/109, Group 2: 0/109 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogrpahy Protocol outcome 6: Infection at duration of study - Actual outcome: Wound related infections at 12 +/- 2 days; Group 1: 1/149, Group 2: 3/151 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 3, Reason: Not treated; Group 2 Number missing: 2, Reason: Not treated Protocol outcome 7: VTE at 7-90 days from hospital discharge - Actual outcome: Total VTE at 12 +/- 2 days; Group 1: 17/109, Group 2: 29/109 Protocol outcome 8: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 12 +/- 2 days; Group 1: 1/109, Group 2: 1/109 Protocol outcome 9: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 12 +/- 2 days; Group 1: 12/109, Group 2: 27/109

Study	Lassen 2007[193]

Protocol outcome 10: DVT (proximal) at 7-90 days from hospital discharge
- Actual outcome: DVT (proximal) at 12 +/- 2 days; Group 1: 3/109, Group 2: 2/109

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN (ALL DOSES) versus WARFARIN (ALL DOSES)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 12 +/- 2 days; Group 1: 1/208, Group 2: 0/109
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogrpahy

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 12 +/- 2 days; Group 1: 21/208, Group 2: 29/109
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogrpahy

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 12 +/- 2 days; Group 1: 1/208, Group 2: 0/109
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogrpahy

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 12 +/- 2 days; Group 1: 4/305, Group 2: 0/151
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 5, Reason: Not treated; Group 2 Number missing: 2, Reason: Not treated

Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy;

Study	Lassen 2007[193]
echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 12 +/- 2 days; Group 1: 1/208, Group 2: 0/109 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 102, Reason: 6 not treated, 40 no venography, 56 un evaluable venography; Group 2 Number missing: 44, Reason: 2 not treated, 9 no venography, 33 un evaluable venogrpahy Protocol outcome 6: Infection at duration of study - Actual outcome: Wound related infections at 12 +/- 2 days; Group 1: 6/305, Group 2: 3/151 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin was open label; Group 1 Number missing: 5, Reason: Not treated; Group 2 Number missing: 2, Reason: Not treated Protocol outcome 7: VTE at 7-90 days from hospital discharge - Actual outcome: Total VTE at 12 +/- 2 days; Group 1: 21/208, Group 2: 29/109 Protocol outcome 8: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 12 +/- 2 days; Group 1: 1/208, Group 2: 1/109 Protocol outcome 9: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 12 +/- 2 days; Group 1: 18/208, Group 2: 27/109 Protocol outcome 10: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 12 +/- 2 days; Group 1: 3/208, Group 2: 2/109	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	RECORD3 trial: Lassen 2008[188]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=2459)
Countries and setting	Conducted in Multiple countries; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 10 to 14 days + Follow-up 30 to 35 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was assessed by ascending bilateral venography. Suspected DVT was confirmed by ultrasonography or venography. Suspected PE was confirmed using ventilation-perfusion scintigraphy of the lung and chest radiography or spiral computed tomography, or pulmonary angiography. Autopsies were planned if a participant died.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (>18 years) who were scheduled for total knee arthroplasty
Exclusion criteria	Active bleeding or high risk of bleeding that contraindicated use of LMWH; contraindication to use of enoxaparin or its dose adjustment; conditions preventing bilateral venography; clinically significant liver disease; concomitant use of protease inhibitors of HIV or fibrinolytic agents; planned intermittent pneumatic compression; requirement of ongoing anticoagulant therapy; pregnancy/breastfeeding
Recruitment/selection of patients	Between February 2006 and November 2006, patients were enrolled in 147 centers in 19 countries
Age, gender and ethnicity	Age - Mean (range): Rivaroxaban 67.6 (28-91) vs. Enoxaparin 67.6 (30-90). Gender (M:F): 781:1678. Ethnicity: White 81.2%; Asian 6.4%; Hispanic 4.1%; Black 1.1%; Other/Unknown 7.2%
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean rivaroxaban 29.5 kg/m2; mean enoxaparin 29.8 kg/m2). 2. Renal impairment: Not applicable
Extra comments	. 3.7% of the participants had a history of VTE
Indirectness of population	No indirectness
Interventions	(n=1254) Intervention 1: Rivaroxaban - Rivaroxaban (all doses). Oral 10mg once daily; initiated 6 to 9 hrs after wound closure; administered every 24 hrs thereafter. Duration At least 10 days up to 14 days. Concurrent medication/care: Dummy placebo injection (n=1277) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Injection 40mg once daily; given 12 hrs before surgery then 6 to 8 hrs after wound closure; administered every 24hrs thereafter. Duration At least 10 days up to 14 days. Concurrent medication/care: Dummy oral placebo tablets

Study	RECORD3 trial: Lassen 2008[188]
Funding	Study funded by industry (Bayer HealthCare; Johnson & Johnson Pharmaceutical Research & Development)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN versus ENOXAPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death up to day 17 at 17 days; Group 1: 0/1201, Group 2: 2/1217; Comments: Absolute risk difference -0.2 (-0.6 to 0.2); p=0.21
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Exception: slight excess of women in the rivaroxaban group (p=0.03); Group 1 Number missing: 53, Reason: Unknown ; Group 2 Number missing: 60, Reason: Unknown
- Actual outcome: Death during follow-up at From day 30 to day 35 after the last dose of study medication; Group 1: 0/1201, Group 2: 4/1217; Comments: Absolute risk difference -0.3 (-0.8 to 0.0); p=0.05
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Exception: slight excess of women in the rivaroxaban group (p=0.03); Group 1 Number missing: 53, Reason: Unknown ; Group 2 Number missing: 60, Reason: Unknown

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT up to day 17 at 17 days; Group 1: 79/824, Group 2: 160/878; Comments: Absolute risk difference -8.4 (-11.1 to -5.2); p<0.001
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Exception: slight excess of women in the rivaroxaban group (p=0.03); Group 1 Number missing: 430, Reason: Unknown ; Group 2 Number missing: 399, Reason: Unknown

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Pulmonary embolism up to day 17 at 17 days; Group 1: 0/1201, Group 2: 4/1217; Comments: Absolute risk difference -0.3 (-0.8 to 0.0); p=0.05
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Exception: slight excess of women in the rivaroxaban group (p=0.03); Group 1 Number missing: 53, Reason: Unknown ; Group 2 Number missing: 60, Reason: Unknown

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at Between start of treatment and 2 days after last dose; Group 1: 21/1254, Group 2: 17/1277; Comments: p=0.77

Study	RECORD3 trial: Lassen 2008[188]
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Exception: slight excess of women in the rivaroxaban group (p=0.03); Group 1 Number missing: 0, Reason: Unknown ; Group 2 Number missing: 0, Reason: Unknown Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding at Between start of treatment and 2 days after last dose; Group 1: 33/1220, Group 2: 28/1239 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Exception: slight excess of women in the rivaroxaban group (p=0.03); Group 1 Number missing: 34, Reason: Unknown ; Group 2 Number missing: 38, Reason: Unknown Protocol outcome 6: Infection at duration of study - Actual outcome: Post-operative infection of wound at Between start of treatment and 2 days after last dose; Group 1: 7/1220, Group 2: 11/1239 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Exception: slight excess of women in the rivaroxaban group (p=0.03); Group 1 Number missing: 34, Reason: Unknown ; Group 2 Number missing: 38, Reason: Unknown Protocol outcome 7: VTE at 7-90 days from hospital discharge - Actual outcome: Symptomatic VTE up to day 17 at 17 days; Group 1: 8/1201, Group 2: 24/1217; Comments: Absolute risk difference -1.3 (-2.2 to -0.4); p=0.005 - Actual outcome: Symptomatic VTE during follow-up at From day 30 to day 35 after the last dose of study medication; Group 1: 5/1201, Group 2: 3/1217; Comments: Absolute risk difference 0.2 (-0.3 to 0.6); p=0.44 Protocol outcome 8: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 17 days; Group 1: 70/824, Group 2: 140/878 Protocol outcome 9: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 17 days; Group 1: 9/824, Group 2: 20/878	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	ADVANCE-1 trial: Lassen 2009[196]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=3195)
Countries and setting	Conducted in Multiple countries; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 10 to 14 days + Follow-up 60 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was assessed using bilateral venography and confirmed by ultrasonography or venography. Suspected PE was confirmed or ruled out using ventilation-perfusion lung scanning, spiral computer tomography or pulmonary angiography. For deaths, when possible, autopsy was carried out.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were scheduled to undergo total knee replacement surgery for one or both knees, including revision of a previously inserted artificial joint
Exclusion criteria	Active bleeding; contraindication to anticoagulant prophylaxis; requirement of ongoing anticoagulant or antiplatelet treatment; uncontrolled hypertension; active hepatobiliary disease; clinically significant impairment of renal function; thrombocytopenia; anaemia; allergy to heparin; allergy to radiographic contrast dye; contraindication to bilateral venography
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (range): Apixaban 65.9 (26-93) vs. Enoxaparin 65.7 (33-89). Gender (M:F): 1212:1983. Ethnicity: White 94.8%; Black 3.8%; Asian 0.8%; Other 0.6%
Further population details	1. BMI : Obese (BMI over 30 kg/m2) (Mean 30 kg/m2). 2. Renal impairment: Not applicable
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=1599) Intervention 1: Apixaban - Apixaban (all doses). Orally 2.5mg twice daily; first doses given at 12 to 24 hrs post-surgery. Duration 10 to 14 days. Concurrent medication/care: Injection of placebo to mimic enoxaparin injection (n=1596) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous injection 30mg every 12 hrs; first doses given at 12 to 24 hrs post-surgery. Duration 10 to 14 days. Concurrent medication/care: Oral placebo tablets to mimic apixaban tablets

Study	ADVANCE-1 trial: Lassen 2009[196]
Funding	Study funded by industry (Bristol-Myers Squibb and Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN versus ENOXAPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death during treatment period at 10 to 14 days; Group 1: 3/1599, Group 2: 3/1596
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Death during follow-up period at Up to 60 days after last dose of study medication; Group 1: 0/1562, Group 2: 3/1554
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37, Reason: Not reported; Group 2 Number missing: 42, Reason: Not reported

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: All DVT during treatment period at 10 to 14 days; Group 1: 89/1142, Group 2: 92/1122; Comments: The numbers of people analysed are the total numbers of patients who had a bilateral venogram that was deemed suitable for evaluation or had a VTE.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 457, Reason: The total number of participants analysed here are all patients who underwent randomisation and received at least one dose of study medication.; Group 2 Number missing: 474, Reason: The total number of participants analysed here are all patients who underwent randomisation and received at least one dose of study medication.

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: All PE during treatment period at 10 to 14 days; Group 1: 17/1599, Group 2: 12/1596
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Adjudicated major bleeding events at 10 to 14 days; Group 1: 11/1596, Group 2: 22/1588; Comments: Difference in risk (95% CI) = -0.81 (-1.49 to 0.14); p=0.05. The total number of participants analysed here are all patients who underwent randomisation and received at least one dose of study medication.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 8

Study	ADVANCE-1 trial: Lassen 2009[196]
Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE during treatment period at 10 to 14 days; Group 1: 2/1599, Group 2: 0/1596 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Adjudicated clinically relevant non-major bleeding events at 10 to 14 days; Group 1: 35/1596, Group 2: 47/1588; Comments: Difference in risk (95% CI) = -0.77 (-1.87 to 0.33). The total number of participants analysed here are all patients who underwent randomisation and received at least one dose of study medication. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 8 Protocol outcome 7: Surgical site haematoma at 7-90 days from hospital discharge - Actual outcome: Haematoma at surgical site at 10 to 14 days; Group 1: 2/1596, Group 2: 2/1588; Comments: The total number of participants analysed here are all patients who underwent randomisation and received at least one dose of study medication. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 8 Protocol outcome 8: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: Symptomatic DVT during follow-up period at Up to 60 days after last dose of study medication; Group 1: 3/1562, Group 2: 2/1554 Protocol outcome 9: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Proximal DVT at Up to 60 days after last dose of study medication; Group 1: 9/1254, Group 2: 11/1207	
Protocol outcomes not reported by the study	Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	ADVANCE-2 trial: Lassen 2010[195]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=3057)
Countries and setting	Conducted in Multiple countries; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 10 to 14 days + Follow-up up to 60 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was assessed with bilateral venography; confirmed by ultrasonography or venography. Suspected PE was assessed with ventilation-perfusion lung scanning, spiral computed tomography or pulmonary angiography. For death, autopsy was performed when possible.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled to have unilateral elective total knee replacement or same-day bilateral knee replacement, including revision
Exclusion criteria	Active bleeding; contraindication to anticoagulant prophylaxis; necessity to continue anticoagulant or antiplatelet treatment; uncontrolled hypertension; active hepatobiliary disease; impaired renal function; thrombocytopenia; anaemia; heparin allergy; allergy to radiographic contrast dye; other disorders preventing bilateral venography
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (IQR): Apixaban 67 (59-73) vs. Enoxaparin 67 (60-73). Gender (M:F): 2216:841. Ethnicity: White 76.1%; Asian 16.6%; Black 1.0%; Hawaiian/Islander 0.07%; Other 3.0%
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI in both groups 29 kg/m2). 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=1528) Intervention 1: Apixaban - Apixaban (all doses). Oral tablets 2.5mg twice daily; first dose given 12 to 24 hrs after wound closure. Duration 10 to 14 days. Concurrent medication/care: Placebo injections to match enoxaparin (n=1529) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous injections 40mg once daily; first injection given 12 hrs before operation then resumed after surgery according to investigators' standard of care. Duration 10 to 14 days. Concurrent medication/care: Placebo tablets to match apixaban
Funding	Study funded by industry (Bristol-Myers Squibb and Pfizer)

Study	ADVANCE-2 trial: Lassen 2010[195]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN versus ENOXAPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death during treatment period at 10 to 14 days; Group 1: 2/1528, Group 2: 0/1529
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Death during follow-up at Up to 60 days; Group 1: 1/1458, Group 2: 1/1469; Comments: The number analysed is the number of randomised patients who entered follow-up.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 70, Reason: Missing participants were those that were randomised but did not enter follow-up.; Group 2 Number missing: 60, Reason: Missing participants were those that were randomised but did not enter follow-up.

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: All DVT during treatment period at 10 to 14 days; Group 1: 142/971, Group 2: 243/997; Comments: The number analysed is the number of patients randomly allocated to treatment who had an adjudicated and assessable bilateral venogram or an adjudicated DVT.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 557, Reason: Participants without an adjudicated and assessable bilateral venogram or an adjudicated DVT were not included in the analysis.; Group 2 Number missing: 532, Reason: Participants without an adjudicated and assessable bilateral venogram or an adjudicated DVT were not included in the analysis.

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: All PE during treatment period at 10 to 14 days; Group 1: 4/1528, Group 2: 0/1529
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: All PE during follow-up at Up to 60 days; Group 1: 3/1458, Group 2: 1/1469; Comments: The number analysed is the number of randomised patients who entered follow-up.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 70, Reason: Missing participants were those that were randomised but did not enter follow-up.v; Group 2 Number missing: 60, Reason: Missing participants were those that were randomised but did not enter follow-up.v

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge

Study	ADVANCE-2 trial: Lassen 2010[195]

- Actual outcome: Adjudicated major bleeding events at 10 to 14 days; Group 1: 9/1501, Group 2: 14/1508; Comments: The number analysed is the number of randomised patients who received the study drugs.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: Those that did not receive any study drug were not included in the safety analysis.; Group 2 Number missing: 21, Reason: Those that did not receive any study drug were not included in the safety analysis.

Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE during treatment period at 10 to 14 days; Group 1: 1/1528, Group 2: 0/1529
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge
- Actual outcome: Adjudicated clinically relevant non-major bleeding events at 10 to 14 days; Group 1: 44/1501, Group 2: 58/1508; Comments: The number analysed is the number of randomised patients who received the study drugs.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: Those that did not receive any study drug were not included in the safety analysis.; Group 2 Number missing: 21, Reason: Those that did not receive any study drug were not included in the safety analysis.

Protocol outcome 7: Surgical site haematoma at up to 45 days from hospital discharge
- Actual outcome: Haematoma at surgical site at 10 to 14 days; Group 1: 1/1501, Group 2: 0/1508; Comments: The number analysed is the number of randomised patients who received the study drugs.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: Those that did not receive any study drug were not included in the safety analysis.; Group 2 Number missing: 21, Reason: Those that did not receive any study drug were not included in the safety analysis.

Protocol outcome 8: VTE at 7-90 days from hospital discharge
- Actual outcome: VTE at 10 to 14 days; Group 1: 13/1195, Group 2: 26/1199

Protocol outcome 9: DVT (symptomatic) at 7-90 days from hospital discharge
- Actual outcome: Symptomatic DVT during follow-up at Up to 60 days; Group 1: 2/1458, Group 2: 1/1469; Comments: The number analysed is the number of randomised patients who entered follow-up.

Study	ADVANCE-2 trial: Lassen 2010[195]
Protocol outcomes not reported by the study	Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Leclerc 1992[200]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=131)
Countries and setting	Conducted in Canada; Setting: Montreal General Hospital, Centre Hospitalier de l'Universite Laval, Sunnybrook Health Science Centre, Hopital du St-Sacrement
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT: confirmed by bilateral contrast venography Major bleeding: defined by any of the following: associated with a drop in haemoglobin of 20g/l or more, requiring transfusion with two or more units of packed red cells or occurring in any of these sites: intracranial, intrao-ocular, retroperitoneal space or intra-articular.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing knee arthroplasty or tibial osteomy
Exclusion criteria	Age less than 40; previous history of DVT or PE, allergy to radiographic contrast material; bleeding disorder; failure to achieve post-operative haemostasis; continuing need for aspirin, non-steroidal anti-inflammatory drugs or oral anticoagulants; active peptic ulcer; pregnancy; haemorrhagic stroke in the previous 3 months; uncontrolled arterial hypertension (systolic ≥200mmHg or diastolic ≥120mmHg); history of heparin induced thrombocytopenia; renal insufficiency (serum creatinine ≥130 umol/l)
Recruitment/selection of patients	Based on inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): 69 years. Gender (M:F): 1/1.5. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Extra comments	Mean duration of surgery: enoxaparin group 139 minutes, placebo group 150 minutes. Type of surgery: tibial osteotomy 19%, cemented arthroplasty 68%, uncemented arthroplasty 13%
Indirectness of population	No indirectness

Study	Leclerc 1992[200]
Interventions	(n=66) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). LMWH, enoxaparin, 30mg every 12 hours. The administration of study medication generally started on the morning of the first post-operative day (day 1) and was continued for 14 days or until discharge. Duration 14 days or until discharge. Concurrent medication/care: The start of treatment was delayed until the evening of day 1 or the morning of day 2, at the latest, for patients who did not achieve haemostasis at the surgical site on the morning of day 1. (n=65) Intervention 2: No treatment - Placebo. 0.4ml of saline every 12 hours. Duration 14 days or until discharge. Concurrent medication/care: The start of treatment was delayed until the evening of day 1 or the morning of day 2, at the latest, for patients who did not achieve haemostasis at the surgical site on the morning of day 1
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 14 days; Group 1: 0/66, Group 2: 0/65
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 14 days; Group 1: 11/65, Group 2: 37/64
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Withdrawal; Group 2 Number missing: 1, Reason: Withdrawal

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 14 days; Group 1: 0/66, Group 2: 1/65
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Surgical site haematoma at up to 45 days from hospital discharge

Study	Leclerc 1992[200]
- Actual outcome: Wound haematoma at 14 days; Group 1: 0/66, Group 2: 1/65 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 14 days; Group 1: 11/65, Group 2: 25/64 Protocol outcome 6: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 14 days; Group 1: 0/65, Group 2: 12/64	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Leclerc 1996[201]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=670)
Countries and setting	Conducted in Canada; Setting: Eight hospitals
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients having knee arthroplasty

Study	Leclerc 1996[201]
Exclusion criteria	Allergy to contrast material; need for oral anticoagulant or antiplatelet agents; bleeding diathesis; gastrointestinal haemorrhage within 3 months of surgery; renal or hepatic insufficiency; uncontrolled hypertension; illicit drug use or alcohol abuse; participation in the present study within the previous 3 months; haemorrhagic stroke within 3 months of surgery; receipt of other investigational drugs in the past month; warfarin allergy
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Warfarin group 69.2 (9.2); LMWH group 68.0 (9.4). Gender (M:F): 1:1.7. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=336) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin (high dose, 30mg twice daily). Therapy began on the morning of the first day after surgery and was administered for 14 days or until hospital discharge, whichever occurred first. Patients also received a warfarin placebo once daily starting the morning of the first day after surgery. Duration 14 days. Concurrent medication/care: No other thromboprophylactic agents or AES were used (n=334) Intervention 2: Vitamin K antagonists - Warfarin (all doses). Warfarin, initial dose not reported. The treatment goal was to maintain the INR between 2-3. Administered from the evening of the operation for 14 days or until hospital discharge, whichever occurred first. Patients also received subcutaneous saline placebo twice daily (every 12 hours). Duration 14 days. Concurrent medication/care: No other thromboprophylactic agents AES were used
Funding	Study funded by industry (Supported by a research grant from Rhone-Poulenc Rorer Canada)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus WARFARIN (ALL DOSES)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 14 days; Group 1: 0/336, Group 2: 0/334
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 14 days; Group 1: 76/206, Group 2: 109/211
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 130, Reason: Inadequate venography ; Group 2 Number missing: 123, Reason: Inadequate

Study	Leclerc 1996[201]
venography Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 14 days; Group 1: 1/336, Group 2: 3/334 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 14 days; Group 1: 6/336, Group 2: 5/334 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Surgical site haematoma at up to 45 days from hospital discharge - Actual outcome: Wound haematoma at 14 days; Group 1: 1/336, Group 2: 1/334 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 14 days; Group 1: 56/206, Group 2: 87/211 Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 14 days; Group 1: 24/206, Group 2: 22/211 Protocol outcome 8: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Surgical site bleeding at 14 days; Group 1: 6/336, Group 2: 5/334	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced

Study	Leclerc 1996[201]
	thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Mirdamadi 2014[225]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=90)
Countries and setting	Conducted in Iran; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention up to 15 days + Follow-up 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Bilateral Doppler sonography was used to detect DVT. Ventilation/perfusion scintigraphy and spiral computed tomography was used to diagnose PE.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients older than 18 years with expected primary TKA
Exclusion criteria	Bleeding diathesis; history of acute intracranial disease / haemorrhagic stroke; major surgery / trauma / uncontrolled hypertension / myocardial infarction within past 3 months; GI / urogenital bleeding / ulcer disease within past 6 months; aspartate aminotransferase / alanine aminotransferase levels higher than twice the upper limit of the normal range within past month; several renal insufficiency; use of NSAID within a week prior to surgery; active malignant disease
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 70 ± 9. Gender (M:F): 38:52. Ethnicity: Implicitly assumed to be all Iranian
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 40mg given 12 hrs before surgery and continued daily. Duration Up to 15 days. Concurrent medication/care: Not reported Comments: Route and frequency of administration not stated (n=45) Intervention 2: Dabigatran - Dabigatran (all doses). First dose of 150mg given 4 hrs after surgery and continued

Study	Mirdamadi 2014[225]
	daily at an increased dose of 225mg. Duration Up to 15 days. Concurrent medication/care: Not reported Comments: Route and frequency of administration not stated
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN versus DABIGATRAN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death during treatment period at 15 days; Group 1: 0/45, Group 2: 0/45
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Only the participants' age, weight and sex are reported and compared. ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: Symptomatic DVT at 15 days; Group 1: 1/45, Group 2: 1/45
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Asymptomatic DVT is not included.; Baseline details: Only the participants' age, weight and sex are reported and compared. ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 0

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Symptomatic PE at 15 days; Group 1: 0/45, Group 2: 0/45
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Asymptomatic PE is not included.; Baseline details: Only the participants' age, weight and sex are reported and compared. ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 0

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 15 days; Group 1: 2/45, Group 2: 3/45; Comments: p=0.66
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Only the participants' age, weight and sex are reported and compared. ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 0

Study	Mirdamadi 2014[225]
Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding at 15 days; Group 1: 7/45, Group 2: 8/45; Comments: p=0.81 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only the participants' age, weight and sex are reported and compared. ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Norgren 1998[241]	RCT	1+	Total: n = 40 Intervention: n = 21 Control: n = 19 11 patients dropped out so results based on 29 patients: Int:15 &	Type of surgery: Patients scheduled for elective knee replacement. Overall M/F: 13/27 Mean age (range): 72 (49-87) years Intervention M/F: 4/11 Control	Type: foot pump (ActOne) mechanical compression plus AES Started evening before surgery, removed during surgery, reapplied	Type: LMWH 40mg once per day Not stated when first dose was administered. used until full mobilisation Additional non-comparative prophylaxis: Not reported	Control: 3mths Int: 3mths	DVT (overall) Confirmed by: venography performed on day 7-10.	Int: 4/15 Control: 0/14 p value: <0.05	Comments: 11 patients dropped out from the study, 5 in the LMWH group and 6 in the foot pump group There were no signs of proximal thrombosis
								Fatal PE Confirmed by autopsy:	Int: 1/15 Control: 0/14 p value: Not significant	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			cont:14	M/F: 7/7	immediately after and continued until full mobilisation. A tourniquet was used during surgery. Additional non-comparative prophylaxis: Not reported					Not reported: PTS, Bleeding related complications, QoL, Survival

Study	RECORD4 trial: Turpie 2009[321]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=3148)
Countries and setting	Conducted in Canada, USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention 11 to 15 days + Follow-up 30 to 35 days after last dose of intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was assessed by ascending bilateral venography. Suspected symptomatic DVT was assessed by ultrasound and confirmed with venography. Suspected PE was confirmed by pulmonary angiography, by ventilation-perfusion lung scintigraphy with chest radiography, or by contrast-enhanced spiral CT.
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	RECORD4 trial: Turpie 2009[321]
Inclusion criteria	Aged 18 years or older and scheduled for TKA
Exclusion criteria	Active / High risk of bleeding; any disorder contraindicating the use of enoxaparin or that might necessitate enoxaparin dose adjustment; disorders preventing bilateral venography; clinically significant liver disease; severe renal impairment; concomitant use of drugs that strongly inhibit cytochrome P450; pregnancy / breastfeeding; planned intermittent pneumatic compression; requirement for ongoing anticoagulant therapy
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Rivaroxaban 64.4 (9.7) vs. Enoxaparin 64.7 (9.7). Gender (M:F): 1060:1974. Ethnicity: White 67.2%; Asian 19.1%; Hispanic 8.3%; Black 5.0%; American Indian 0.2%; Other / Missing data 0.2%
Further population details	1. BMI : Obese (BMI over 30 kg/m2) (Mean BMI 31 kg/m2). 2. Renal impairment: Not applicable
Indirectness of population	No indirectness: Prevalence and incidence of VTE are found to be lower in Asian populations. The proportion of Asians amongst the study participants is higher than what would normally be expected in studies from Europe.
Interventions	(n=1584) Intervention 1: Rivaroxaban - Rivaroxaban (all doses). Oral 10mg once daily; started 6 to 8 hrs after wound closure or after adequate haemostasis had been achieved; then every 22 to 26 hrs in the evening thereafter. Duration 11 to 15 days. Concurrent medication/care: Placebo injections to match enoxaparin every 12 hrs (n=1564) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous injections 30mg; started 12 to 24 hrs after wound closure; then every 10 to 14 hrs thereafter. Duration 11 to 15 days. Concurrent medication/care: Placebo tablets to match rivaroxaban every 24 hrs
Funding	Study funded by industry (Bayer Schering Pharma AG, Johnson & Johnson Pharmaceutical Research & Development)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN versus ENOXAPARIN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death during treatment period at Up to day 17; Group 1: 2/1526, Group 2: 3/1508; Comments: ARD -0.07 (-0.46 to 0.30); p=0.74
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis.; Group 2 Number missing: 56, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis.
- Actual outcome: Death during follow-up period at Up to day 35; Group 1: 4/1526, Group 2: 3/1508; Comments: ARD 0.06 (-0.35 to 0.50); p=0.80
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis.; Group 2 Number missing: 56, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis.

Study	RECORD4 trial: Turpie 2009[321]

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: All DVT during treatment period at Up to day 17; Group 1: 61/965, Group 2: 86/959; Comments: The number analysed is the modified intention-to-treat population, which consisted of all patients who had taken at least one dose of study medication, had also undergone the planned surgery and had an adequate assessment for thromboembolism.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Missing data was of those participants who were not included in the "modified ITT population". They were excluded because they did not receive any study medication and they either had incomplete assessment or did not have a planned surgery.; Group 2 Number missing: 605, Reason: Missing data was of those participants who were not included in the "modified ITT population". They were excluded because they did not receive any study medication and they either had incomplete assessment or did not have a planned surgery.

Protocol 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE during treatment period at Up to day 17; Group 1: 5/1526, Group 2: 8/1508; Comments: ARD -0.20(-0.75 to 0.30); p=0.53
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis.; Group 2 Number missing: 56, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis.

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding events during treatment period at Between start of treatment and 2 days after last dose; Group 1: 27/1584, Group 2: 16/1564; Comments: The number analysed is the safety population, which is the number of participants who had taken at least one dose of study medication. p=0.11
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge
- Actual outcome: Clinically relevant non-major bleeding events at Between start of treatment and 2 days after last dose; Group 1: 39/1526, Group 2: 30/1508; Comments: The number analysed is the safety population, which is the number of participants who had taken at least one dose of study medication.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis.; Group 2 Number missing: 56, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis.

Study	RECORD4 trial: Turpie 2009[321]
Protocol outcome 6: Infection at duration of study - Actual outcome: Postoperative wound infection at Unclear; Group 1: 4/1526, Group 2: 3/1508 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis.; Group 2 Number missing: 56, Reason: Those missing did not take any study medication and was therefore not included in the safety analysis. Protocol outcome 7: VTE at 7-90 days from hospital discharge - Actual outcome: Symptomatic VTE during follow-up period at Up to day 17; Group 1: 11/1526, Group 2: 18/1508; Comments: ARD -0.47 (-1.16 to 0.23); p=0.19 - Actual outcome: Major VTE at up to day 17; Group 1: 11/1011, Group 2: 15/1020 Protocol outcome 8: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at up to day 17; Group 1: 6/965, Group 2: 10/959 Protocol outcome 9: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at up to day 17; Group 1: 52/965, Group 2: 63/959 Protocol outcome 10: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at up to day 17; Group 1: 3/965, Group 2: 13/959 Protocol outcome 11: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at Between start of treatment and 2 days after last dose; Group 1: 1/1526, Group 2: 0/1508	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Warwick 2002 [334]			Total: 229 Intervention: n = 117 Control: n = 112	Type of surgery: Patients undergoing total knee replacement(TKR). All patients had AES fitted below the knee before surgery Intervention: Mean age:73±9 M/F:43/74 Control: Mean age: 71±10 M/F:37/75 Pre-existing risk factors: Previous thomboembolism: Int: n = 7, control:n = 4, Smoking, varicose veins	A- V impulse foot pump Additional non-comparative prophylaxis: Not reported	Enoxaparin - LMWH	3 months	DVT (overall) Confirmed by: Ascending venography on 6th & 8th day	Analysis based on number of patients who completed venography Int: 57/99 Control: 48/89 p value: Not significant	Study concluded that there neither method provided superior prophylaxis. All patient completed follow-up but only 99 in the intervention and 89 in the control were available for venography 4 patients were said to have PE but paper did not state which groups they belonged Not reported: PTS, QoL, Survival
								Proximal vein thrombosis	Int: 4/99 Control: 0/89 p value: Not significant	
								Fatal PE Confirmed by:	Int: 2/99 Control: 0/89 p value: Not significant	
								Bleeding related complications	Int: 0/99 Control: 4/89 p value: Not significant	

Study	Wilson 1992[339]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in United Kingdom; Setting: Kings College Hospital, London
Line of therapy	Not applicable
Duration of study	Intervention time: Unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT: confirmed by ascending ipsilateral venography PE: confirmed by ventilation perfusion lung scanning
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing elective total knee replacements with Biomet AGC 2500 or Insall-Burstein prostheses and a standard technique.
Exclusion criteria	Not reported
Recruitment/selection of patients	Based on inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): 71 years. Gender (M:F): 1/3. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Renal impairment: Not applicable
Extra comments	Duration of surgery: foot pump group 139 minutes, control group 132 minutes
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Foot pumps or foot impulse devices - Foot pumps. A-V impulse system, device is an electrically driven air compressor with reservoir that intermittently inflates a pneumatic pad apploed over stockinette to the sole of the foot and held in place by a slipper. The compressor rapidly inflates the pad (0.4 seconds) and then deflates it after a period of three seconds. Duration Not clearly reported. Concurrent medication/care: N/A (n=32) Intervention 2: No treatment - Usual care. Control group, no further details reported. Duration Not clearly reported. Concurrent medication/care: N/A
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOOT PUMPS versus USUAL CARE	

Study	Wilson 1992[339]
Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 10 days; Group 1: 5/28, Group 2: 19/32 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Time-point not reported; Group 1: 0/28, Group 2: 0/32 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: DVT (distal) at 10 days; Group 1: 5/28, Group 2: 13/32 Protocol outcome 4: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: DVT (proximal) at 10 days; Group 1: 0/28, Group 2: 6/32	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

Study	Zou 2014[349]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=324)
Countries and setting	Conducted in China; Setting: Affiliated Hospital of Qingdao University, China
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 14 days + 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by colour Doppler ultrasonography
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients who were diagnosed with knee osteoarthritis, initially underwent unilateral total knee arthroplasty, were DVT-negative according to the preoperative colour Doppler ultrasonography on the deep veins of both lower extremities and gave informed consent for the therapeutic schedule.
Exclusion criteria	The exclusion criteria were as follows: patients who had a history of haemorrhagic disease or a bleeding tendency during the preoperative coagulation test, had a medical history of VTE, were infused with over 2000ml of fluids 24 hours after surgery, underwent knee arthroplasty, or used a combination of other drugs that might impact the findings
Recruitment/selection of patients	Between July 2011 and July 2013
Age, gender and ethnicity	Age - Mean (range): LMWH group 65.7 (54-80) years; Rivaroxaban group 63.5 (50-82) years; Aspirin 62.7 (47-79) years. Gender (M:F): 1/2.7. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean: 27.4). 2. Renal impairment: Not applicable
Extra comments	Operation time (mean): 87 minutes
Indirectness of population	No indirectness
Interventions	(n=112) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). LMWH, enoxaparin, 4000IU (0.4ml)/40mg once daily (standard dose) subcutaneously given. Administered from 12 hours after the operation and continued for 14 days. . Duration 14 days. Concurrent medication/care: Medical parapatellar approach with a tourniquet (pressure of 260 mmHg) was used. Patients were given antibiotics by intravenous drip for 3 days to prevent infections and oral Celecoxib capsules for analgesia after surgery. A pressure dressing was applied to the affected extremities with elastic bandages and the affected extremities were elevanted. Ankle pump exercise began 6 hours after surgery. Mobilisation started 1 day after surgery, they practiced walking with walking aids two or three times a day 2 days after surgery for

Study	Zou 2014[349]
	10-20 minutes each time. (n=102) Intervention 2: Rivaroxaban - Rivaroxaban (all doses). Rivaroxaban, 10mg, once daily, subcutaneously given. Administered from 12 hours after the operation and continued for 14 days. . Duration 14 days. Concurrent medication/care: Medical parapatellar approach with a tourniquet (pressure of 260 mmHg) was used. Patients were given antibiotics by intravenous drip for 3 days to prevent infections and oral Celecoxib capsules for analgesia after surgery. A pressure dressing was applied to the affected extremities with elastic bandages and the affected extremities were elevanted. Ankle pump exercise began 6 hours after surgery. Mobilisation started 1 day after surgery, they practiced walking with walking aids two or three times a day 2 days after surgery for 10-20 minutes each time. (n=110) Intervention 3: Aspirin - Aspirin (up to 300mg). Aspirin, 100mg, once daily, subcutaneously given. Administered from 12 hours after the operation and continued for 14 days. . Duration 14 days. Concurrent medication/care: Medical parapatellar approach with a tourniquet (pressure of 260 mmHg) was used. Patients were given antibiotics by intravenous drip for 3 days to prevent infections and oral Celecoxib capsules for analgesia after surgery. A pressure dressing was applied to the affected extremities with elastic bandages and the affected extremities were elevanted. Ankle pump exercise began 6 hours after surgery. Mobilisation started 1 day after surgery, they practiced walking with walking aids two or three times a day 2 days after surgery for 10-20 minutes each time.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (40MG) versus RIVAROXABAN

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 28 days (4 weeks); Group 1: 14/112, Group 2: 3/102
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge

Study	Zou 2014[349]
- Actual outcome: PE at 28 days (4 weeks); Group 1: 0/112, Group 2: 0/102 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (40MG) versus ASPIRIN (UP TO 300MG) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 28 days (4 weeks); Group 1: 14/112, Group 2: 18/110 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 28 days (4 weeks); Group 1: 0/102, Group 2: 0/110 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN versus ASPIRIN (UP TO 300MG) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 28 days (4 weeks); Group 1: 3/102, Group 2: 18/110 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 28 days (4 weeks); Group 1: 0/102, Group 2: 0/110 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal);

Study	Zou 2014[349]
	results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Surgical site haematoma at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study;

H.25 Non-arthroplasty orthopaedic knee surgery

Study	Camporese 2008[41]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1761)
Countries and setting	Conducted in Italy; Setting: Department of Knee Surgery of the Abano Terme Clinic and the Unit of Angiology of the University Hospital of Padua
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All consecutive outpatients having a diagnostic arthroscopy or assisted knee surgery for partial meniscectomy, cartilage shaving, cruciate ligament reconstruction, synovial resection or combined surgical procedures
Exclusion criteria	Patients younger than 18 years of age, pregnant, previous venous thromboembolism, active cancer, known thrombophilia, receiving mandatory anticoagulation, hypersensitive to LMWH, recent major bleeding event, severe renal or hepatic failure, anticipated poor adherence, geographic inaccessibility, or tourniquet thigh time greater than 1 hour

Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): AES group: 42.3 (14.4), LMWH 14 days: 42.5 (16.7), LMWH 7 days: 41.9 (15.1). Gender (M:F): AES group: 1.66:1, LMWH 14 days: 1.60:1, LMWH 7 days: 1.62:1. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Cancer status: No active cancer 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=660) Intervention 1: Anti-embolism stockings - Above knee. AES full length on the operated leg for 7 days, application before weight bearing. Duration 7 days. Concurrent medication/care: Not reported (n=444) Intervention 2: Low molecular weight heparin (not licensed in UK) - Nadroparin (2850 units once daily - up to 57 units/kg once daily). Nadroparin, 3800U, subcutaneously once daily. First dose at hospital 8 hours after the procedure. Duration 14 days. Concurrent medication/care: Not stated (n=657) Intervention 3: Low molecular weight heparin (not licensed in UK) - Nadroparin (2850 units once daily - up to 57 units/kg once daily). Nadroparin, 3800U, subcutaneously once daily. First dose at hospital 8 hours after the procedure. Duration 7 days. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NADROPARIN (2850 UNITS ONCE DAILY - UP TO 57 UNITS/KG ONCE DAILY) EXTENDED DURATION versus ABOVE KNEE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 8 days; Group 1: 0/444, Group 2: 0/660; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 8 days; Group 1: 9/444, Group 2: 29/660; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 8 days; Group 1: 2/444, Group 2: 2/660; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening

clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 8 days; Group 1: 1/444, Group 2: 1/660; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: DVT (symptomatic) at 7-90 days from hospital discharge
- Actual outcome: DVT symptomatic at 8 days; Group 1: 2/444, Group 2: 12/660; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 6: DVT (distal) at 7-90 days from hospital discharge
- Actual outcome: DVT distal at 8 days; Group 1: 8/444, Group 2: 21/660; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 7: DVT (proximal) at 7-90 days from hospital discharge
- Actual outcome: DVT proximal at 8 days; Group 1: 1/444, Group 2: 8/660; Risk of bias: ; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NADROPARIN (2850 UNITS ONCE DAILY - UP TO 57 UNITS/KG ONCE DAILY) EXTENDED DURATION versus NADROPARIN (2850 UNITS ONCE DAILY - UP TO 57 UNITS/KG ONCE DAILY) STANDARD DURATION

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 8 days; Group 1: 0/444, Group 2: 0/657; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 8 days; Group 1: 9/444, Group 2: 10/657; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 8 days; Group 1: 2/444, Group 2: 2/657; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 8 days; Group 1: 1/444, Group 2: 2/657; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NADROPARIN (2850 UNITS ONCE DAILY - UP TO 57 UNITS/KG ONCE DAILY) STANDARD DURATION versus ABOVE KNEE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge

- Actual outcome: All-cause mortality at 8 days; Group 1: 0/657, Group 2: 0/660; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 8 days; Group 1: 10/657, Group 2: 29/660; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 8 days; Group 1: 2/657, Group 2: 2/660; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 8 days; Group 1: 2/657, Group 2: 1/660; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study; Unplanned return to theatre at up to 45 days from hospital discharge

Study	Camporese 2016[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=241)
Countries and setting	Conducted in Italy; Setting: Nine Italian hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 days + 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged at least 18 years, scheduled for non-diagnostic arthroscopy assisted knee surgery, not combined with open surgery
Exclusion criteria	Concomitant strong concurrent CYP3A4-inhibitors and/or P=gp-inhibitors; proven hypersensitivity to the study drug; pregnancy or lactation; advanced hepatic disease (child-Pugh B and C); known thrombophilia; mandatory anticoagulation; previous objectively documented VTE; known severe bleeding tendency; clinically significant active bleeding; severe renal failure (creatinine clearance <30ml/min estimate with the Cockcroft-Gault method); recent (6-12 weeks) major surgery; current involvement in another clinical trial
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Rivaroxaban group: 44.9 (12.8); control group 45.9 (13.9). Gender (M:F): 162:89. Ethnicity: Not reported
Further population details	1. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI: rivaroxaban 27.6 (16.0); control 28.1 (20.7)). 2. Cancer status: Not applicable 3. Renal impairment: No renal impairment (eGFR greater than 30ml/min/1.73m2)
Indirectness of population	No indirectness
Interventions	(n=122) Intervention 1: Rivaroxaban - Rivaroxaban (all doses). Rivaroxaban (10mg, once daily). Started 8-10 hours postoperatively, for 6 days. Duration 6 days. Concurrent medication/care: The use of any other prophylactic regimen such as LMWH and/or AES, was strongly discouraged throughout the study period (n=119) Intervention 2: No treatment - Placebo. Placebo, started 8-10 hours postoperatively for 6 days. Duration 6 days . Concurrent medication/care: The use of any other prophylactic regimen such as LMWH and/or AES, was strongly discouraged throughout the study period
Funding	Study funded by industry (Bayer SpA provided the study drugs and covered the insurance costs)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN (ALL DOSES) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 3 months; Group 1: 0/120, Group 2: 0/114
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 5

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 3 months; Group 1: 2/120, Group 2: 8/114
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 5

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 3 months; Group 1: 0/120, Group 2: 0/114
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 5

Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 3 months; Group 1: 0/120, Group 2: 0/114
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 5

Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study; Unplanned return to theatre at up to 45 days from hospital discharge

Study	Marlovits 2007[216]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=175)
Countries and setting	Conducted in Austria; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 23-28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People having arthroscopic ACL asurgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 19-55 years with a maximum weight of 100kg who were admitted to the hospital for arthroscopic ACL surgery
Exclusion criteria	Patients were excluded if they had participated in another clinical trial in the 4 weeks before this trial, if they had a diagnosis of DVT confirmed by magnetic resonance venography on admission, were receiving oral anticoagulation therapy, or were allergic to heparin, presence of haemophilia, or other blood disorders, pregnancy, and presence of any other serious illness such as proliferative diabetic retinopathy, liver or pancreatic illness, multiple trauma, uncontrollable hypertension or endocarditis lenta
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Extended: 29.9 (7.4), standard group: 30.2 (6.9). Gender (M:F): 108:67. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Cancer status: Not applicable 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=87) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 40mg, subcutaneously, once daily, starting 12-18 hours preoperatively and continuing for 3-8 days in hospital after surgery. Followed by an additional 20 days treatment. Duration 23-28 days. Concurrent medication/care: Not reported (n=88) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 40mg, subcutaneously, once daily, starting 12-18 hours preoperatively and continuing for 3-8 days in hospital after surgery. Followed by a placebo for an additional 20 days. Duration 23-28 days. Concurrent medication/care: Not reported
Funding	Study funded by industry (Supported by an educational grant from SanofiAventis, Paris, France)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) EXTENDED DURATION versus ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) STANDARD DURATION Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 23-28 days; Group 1: 2/72, Group 2: 28/68; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 23-28 days; Group 1: 0/72, Group 2: 0/68; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 23-28 days; Group 1: 0/72, Group 2: 0/68; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study; Unplanned return to theatre at up to 45 days from hospital discharge

Study	POST-KAST trial: Van Adrichem 2017[322]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1543)
Countries and setting	Conducted in Netherlands; Setting: 10 hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Minor arthroscopic surgery (combined anaesthetic and surgery less than 1 hour):
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients 18 years of age or older who were scheduled to undergo knee arthroscopy for meniscectomy, diagnostic arthroscopy, removal for loose bodies, or other indications
Exclusion criteria	History of venous thromboembolism, contraindications to LMWH therapy, pregnancy, and current use of anticoagulant therapy for other indications
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Treatment group: 48.1 (12.8), control group: 49.1 (12.3). Gender (M:F): 810:641. Ethnicity: Not reported
Further population details	1. BMI : Mixed (20.7% obese (BMI >30)). 2. Cancer status: Not applicable (Mixed (0.8% <1 year before enrolment)). 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=773) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). LMWH once daily for the 8 days after arthroscopy, the first dose was administered postoperatively but before discharge on the day of surgery. The drug was nadroparin or dalteparin (according to the preference of the hospital). A dose of 2850U nadroparin, or 2500U dalteparin (a double dose was used for those who weighed more than 100kg). Duration 8 days. Concurrent medication/care: Not reported (n=770) Intervention 2: No treatment - Usual care. No anticoagulant therapy. Duration Not reported. Concurrent medication/care: Not reported
Funding	Academic or government funding (Supported by the Netherlands Organisation for Health Related and Development)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus USUAL CARE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome for Minor arthroscopic surgery (combined anaesthetic and surgery less than 1 hour): All-cause mortality at 3 months; Group 1: 0/731, Group 2: 0/720; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome for Minor arthroscopic surgery (combined anaesthetic and surgery less than 1 hour): DVT at 3 months; Group 1: 4/731, Group 2: 2/720; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome for Minor arthroscopic surgery (combined anaesthetic and surgery less than 1 hour): PE at 3 months; Group 1: 1/731, Group 2: 1/720; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome for Minor arthroscopic surgery (combined anaesthetic and surgery less than 1 hour): DVT at 3 months; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study; Unplanned return to theatre at up to 45 days from hospital discharge

Study	Wirth 2001[341]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=239)
Countries and setting	Conducted in Germany; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients scheduled for knee arthroplasty
Stratum	Major arthroscopic surgery (combined anaesthetic and surgery longer than 1 hour): Mean duration of anaesthesia: 68 (46) minutes
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for knee arthroplasty
Exclusion criteria	Patients were excluded if they were pregnant, younger than 18 years, had personal history of DVT, or if there was a contraindication to contrast venography or trial medication
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 37.6 (13.0), control group: 38.5 (11.6). Gender (M:F): 179:60. Ethnicity: Not reported
Further population details	1. BMI : Not applicable 2. Cancer status: Not applicable 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=117) Intervention 1: Low molecular weight heparin (not licensed in UK) - Reviparin (1750 units once daily - 4200 units once daily). Reviparin, 1750U injected subcutaneously once daily. Duration Mean (SD): 8.1 (11.3) days. Concurrent medication/care: Not reported (n=122) Intervention 2: No treatment - Usual care. No drug treatment for prevention of thromboembolism, consistent with usual practice. Duration Not reported. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REVIPARIN (1750 UNITS ONCE DAILY - 4200 UNITS ONCE DAILY) versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome for Major arthroscopic surgery (combined anaesthetic and surgery longer than 1 hour): DVT at 10 days; Group 1: 1/117, Group 2: 5/122; Risk of bias:

High; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome for Major arthroscopic surgery (combined anaesthetic and surgery longer than 1 hour): PE at 10 days; Group 1: 0/117, Group 2: 0/122; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome for Major arthroscopic surgery (combined anaesthetic and surgery longer than 1 hour): Major bleeding at 10 days; Group 1: 0/117, Group 2: 0/122; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 4: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome for Major arthroscopic surgery (combined anaesthetic and surgery longer than 1 hour): Clinically relevant non-major bleeding at 10 days; Group 1: 1/117, Group 2: 4/122; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: DVT (distal) at 7-90 days from hospital discharge - Actual outcome for Major arthroscopic surgery (combined anaesthetic and surgery longer than 1 hour): DVT (distal) at 10 days; Group 1: 1/117, Group 2: 5/122; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Infection at duration of study; Unplanned return to theatre at up to 45 days from hospital discharge

H.26 Foot and ankle orthopaedic surgery

No relevant clinical studies were identified.

H.27 Upper limb orthopaedic surgery

No relevant clinical studies were identified.

H.28 Spinal surgery

Study	Du 2015[88]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=665)
Countries and setting	Conducted in China; Setting: Department of Orthopedic Surgery, Qilu Hospital and the department of Spine Surgery, Yantaishan Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by Doppler ultrasonography. Spiral computed tomography (CT) was conducted as soon as possible to determine pulmonary angiography. Major bleeding was defined as fatal bleeding, bleeding in inflow critical organs (such as the posterior peritoneum, intracranium, intraocular, and intraspinal canal), bleeding-induced reoperation, or clinically significant bleeding outside the surgical site with a decrease of ≥20 g/L in hemoglobin level (with the level from the first postoperative day as the reference value), or the need to transfuse ≥2 units of whole blood or packed red blood cells. Clinically relevant non-major bleeding included skin bruising, gastrointestinal bleeding, fecal occult blood, and urine erythrocytes) during the treatment and bleeding wound complications (a composite indicator of wound hematoma and surgical site bleeding).
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who underwent lumbar surgery
Exclusion criteria	1) oral anticoagulant therapy 3 months prior to the operation; 2) vein thrombosis on preoperative B-ultrasound; 3) preoperative urinalysis positive for red blood cells, fecal occult blood, skin purpura, or hematoma; 4) active bleeding or high risk of bleeding; and 5) contraindication towards rivaroxaban and parnaparin or patients whose parnaparin dose needed to be adjusted
Recruitment/selection of patients	Patients who underwent lumbar surgery between August 2009 and December 2012
Age, gender and ethnicity	Age - Mean (SD): ≥60 years, 40% (no further details reported). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. BMI: Obese (BMI over 30 kg/m2) (46% of participants had a BMI ≥30 kg/m2). 3. Renal impairment: Not applicable 4. Weight bearing: Not applicable
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=324) Intervention 1: Low molecular weight heparin (not licensed in UK) - Parnaparin (3200 units once daily - 4250 units once daily). Patients received subcutaneous injections of 40 mg parnaparin (Sanofi-Aventis, France 1–13, Boulevard Romain Rolland 75014 Paris, France) 6 to 8 h after surgery and once per day until the 14th day, when they could fully ambulate. Duration 14 days. Concurrent medication/care: N/A (n=341) Intervention 2: Rivaroxaban - Rivaroxaban (all doses). Patients began daily oral treatment with 10 mg rivaroxaban (Bayer Schering Pharma AG, Leverkusen, D-51368, Germany) 6 to 8 h after surgery, and the treatment continued until the 14th day, when the patients could fully ambulate. Duration 14 days. Concurrent medication/care: N/A
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARNAPARIN versus RIVAROXABAN

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 14 days; Group 1: 1/324, Group 2: 0/341; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 14 days; Group 1: 8/324, Group 2: 6/341; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 14 days; Group 1: 1/324, Group 2: 1/341; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 14 days; Group 1: 1/324, Group 2: 2/341; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding at 14 days; Group 1: 6/324, Group 2: 6/341; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: VTE at 7-90 days from hospital discharge - Actual outcome: VTE (symptomatic) at 14 days; Group 1: 6/324, Group 2: 3/341; Protocol outcome 7: DVT (distal) at 7-90 days from hospital discharge - Actual outcome: Distal DVT at 14 days; Group 1: 5/324, Group 2: 4/341; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 8: DVT (proximal) at 7-90 days from hospital discharge - Actual outcome: Proximal DVT at 14 days; Group 1: 3/324, Group 2: 2/341; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 9: Fatal bleeding at 45 days from hospital discharge - Actual outcome: Fatal bleeding at 14 days; Group 1: 0/324, Group 2: 0/341; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 10: Site of bleeding (gastrointestinal ; surgical site; brain/spine; other) at 45 days from hospital discharge - Actual outcome: Reoccurrence of surgical bleeding at 14 days; Group 1: 0/324, Group 2: 1/341; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: Bleeding into important organs at 14 days; Group 1: 0/324, Group 2: 1/341; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Unplanned return to theatre at up to 45 days from hospital discharge

Study	Wood 1997[343]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=134)
Countries and setting	Conducted in USA; Setting: Twin Cities Scoliosis Spine Center, USA
Line of therapy	Not applicable
Duration of study	Not clear: Patients used the interventions till hospital discharge - length of stay not reported
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT confirmed by duplex ultrasonography. No confirmation technique reported for PE
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients having major thoracolumbar reconstructive spinal procedures. Major reconstructive spinal procedures were defined as those involving anterior or posterior (or both) thoracic, lumbar, or thoracolumbar spine fusions or multilevel decompressions, or a combination of these.
Exclusion criteria	Patients were excluded if they had: cervical procedures, diskectomies, laminectomies, hardware removal, irrigation and debridements, and posterior spine decompressions of only one level. Patients were excluded with a history of DVT or who preoperatively had such a medical risk for DVT as to require prophylaxis. Patients also were excluded from the study if they had a history of any of the following: pulmonary embolism, congestive heart failure, previous treatment with anticoagulants, or external conditions precluding the application of compression devices such as infection, neuropathy, or chronic venous stasis.
Recruitment/selection of patients	Between March 1, 1994, and April 1, 1995
Age, gender and ethnicity	Age - Mean (SD): 39.5 years. Gender (M:F): 1.4/1. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. BMI : Not applicable 3. Renal impairment: Not applicable 4. Weight bearing: Not applicable
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Foot pumps or foot impulse devices - Foot pumps. Patients wore AES (thigh-length) in addition to foot wraps/foot pumps. AES was placed on all patients shortly before and during surgery and were worn for the remainder of the hospital course. Foot wraps were worn during and after surgery. Foot wraps used were inflatable wraps and were secured around and under the arch of each foot and behind the ankle and connected through tubing to

	a pneumatic control unit that generated cyclic intermittent compression. Inflation was <0.4 seconds, and the cycle is repeated every 20 seconds. Duration Until discharge (time-point not reported). Concurrent medication/care: Patients were moved from bed to chair as soon as they were able, typically on the next day. They then began ambulating on day 1, 2, 3 or occasionally 4. The thigh-high stocking were worn at all times, except for bathing. (n=59) Intervention 2: Intermittent pneumatic compression devices - Below knee. Patients wore graduated compression stockings and a sequential pneumatic compression wrap (IPCD). AES were placed on all patients short before and during the surgery and were worn for the remainder of the hospital course. Compression devices were worn post-operatively until ambulation was resume and, thereafter, when in bed until discharge. Duration Until discharge (time-point not reported). Concurrent medication/care: Patients were moved from bed to chair as soon as they were able, typically on the next day. They then began ambulating on day 1, 2, 3 or occasionally 4. The thigh-high stocking were worn at all times, except for bathing.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOOT PUMPS versus IPCD (ABOVE-KNEE) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 5-7 days; Group 1: 0/75, Group 2: 0/59; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 5-7 days; Group 1: 0/75, Group 2: 0/59; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Health-related quality of life (validated scores only) at up to 90 days from hospital discharge - Actual outcome: Visual analogue comfort scale at Hospital discharge - time-point not reported; Group 1: mean 5.84 cm (SD 2.8); n=75, Group 2: mean 5.56 cm (SD 2.9); n=59; Visual analogue comfort scale 0-10 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major

	bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study; Unplanned return to theatre at up to 45 days from hospital discharge

H.29 Cranial surgery

Study	**Cerrato 1978[46]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Italy; Setting: Neurological Institute of Milan, Italy
Line of therapy	Not applicable
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed by fibrinogen test using a Pitaman 235 isotope localisation
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People underwent elective intracranial surgical procedures; all over 40 years of age;
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 52 years. Gender (M:F): 1/1. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. BMI : Not applicable 3. Mobility: Not applicable 4. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH (calcium heparin), 5000IU subcutaneously administered every 8 hours. Duration 7 days. Concurrent medication/care: 5000IU was considered to be a safe prophylactic dose if the patient's plasma heparin concentration was less than 0.18 units/ml 3 hours after administration. Otherwise, a lower dose was given and the patient's plasma heparin concentration was tested again after 3 hours. Once established, the safe prophylactic dose was given 2 hours before

Study	Cerrato 1978[46]
	surgery and every 8 hours thereafter for at least 7 days. Indirectness: No indirectness (n=50) Intervention 2: No treatment - Placebo. No VTE prophylaxis (further details not provided). Duration 7 days. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN versus CONTROL GROUP Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 8 days; Group 1: 3/50, Group 2: 17/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Collins	Systematic	1+	Total:	People having	UFH 5000U,	No	8 days	DVT	Int: 3/50	Not

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
1988 [65] 74 studies included, 1 included in this review - Cerrato 1978[46]	Review		100 Intervention : 50 Control: 50 7486	elective neurosurgery	given 2 hours before surgery and 3x daily after for at least 7 days	prophylaxis		confirmed by radiolabelled fibrinogen	Cont: 17/50	reported: Funding, QoL, LoS or PTS. Event rates reported here are for all studies as published in the systematic review.

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Dickinson 1998[84]	RCT	1+	Total: 66 Int1: n= 21 Int 2: n=23 Control: n=22	Type of surgery: Neurosurgery for intracranial neoplasms Intervention 1: Mean age: 43 (28-61) yrs Intervention 2: Mean age: 50 (29-	Int 1: LWMH (Enoxaparin) Dose: administered subcutaneously at a dose of 30mg in the anaesthesia holding room. He dose was continued at a dose of 30mg every 12 hours	Type: Thigh high sequential compression device Timing: started before induction of	1 month	DVT Confirmed by: duplex imaging (on four occasions in the first 1 month after surgery) Symptomatic PE	Int 1: 1/21 Control: 3/22 p value = 0.53 Int 2: 4/23 Comp: 3/22 P=0.90 Int 1: 0/21 Int 2: 0/23 Comp: 0/22	Comments: Study terminated early when it was determined that the enoxaparin treated groups exhibited a greater

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				72) yrs Control: Mean age: 49 (20-72) M/F numbers not reported Pre-existing Risk Factors: Not reported Excluded patients: history of DVT or PE, allergy to heparin or other anticoagulant agents, history of surgery or major trauma to the lower extremities, concurrent condition requiring anticoagulation therapy; cranial base neoplasms and pituitary adenomas	Int 2: Combination of Enoxaparin and SCD Dose: as before Timing: started before induction of anaesthesia until discharge from Neurosurgery Service. Additional non-comparative prophylaxis: AES on lower extremities at time of admission to the hospital Int 2: Combination of LMWH and thigh high sequential compression device.	anesthesia and continued postoperatively until patient was walking without assistance Additional non-comparative prophylaxis: AES on lower extremities at time of admission to the hospital		Bleeding related complications (intracerebral haemorrhage or epidural haematoma)	Int 1: 2/21 Int 2: 3/23 Comp: 0/22	incidence of postoperative neurological deficits secondary to intracranial haemorrhage. Not reported: Post thrombotic leg, length of stay. Funding: NR
								Mortality	Int 1: 0/21 Int 2: 1/23 Comp: 1/22	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Goldhaber 2002[121]	RCT	1+	Total: 150 Intervention: n = 75 (DVT assessed in) Control: n = 75 (DVT assessed in)	Type of surgery: Patients undergoing craniotomy with suspected or metastatic brain tumour Excluded people with a history of overt bleeding, heparin allergy or VTE within the prior 6 months Intervention: Mean age: 48.33 (+15.07) yrs M/F:39/36 Control: Mean age: 48.87 (+12.52) yrs M/F:40/35 Pre-existing risk	Type: LMWH (Enoxaparin) Dose: 40mg/ in the morning, placebo in the evening Timing: Begun morning of 1st postoperative day and continued until discharge or VTE diagnosed. Additional non-comparative prophylaxis: AES (73/75 participants) intermittent pneumatic compression devices (72/75 participants)	Type: UFH Dose: 5000 IU twice per day Timing: Begun morning of 1st postoperative day and continued until discharge or VTE diagnosed. Additional non-comparative prophylaxis: AES (72/75 participants) intermittent pneumatic compression devices (71/75 participants)	30 days	DVT Confirmed by duplex ultrasonography	Int: 9/75 Control: 5/75 p value: 0.401	Patients scanned one day prior to, or on day of discharge Funding Research grant from Aventis Not reported: PTS, QoL
								Symptomatic DVT Confirmed by duplex ultrasonography	Int: 0/75 Control: 0/75 p value: not sig	
								Proximal DVT Confirmed by duplex ultrasonography	Int: 2/75 Control: 2/75 p value: 1	
								Unilateral calf DVT Confirmed by duplex ultrasonography	Int: 6/75 Control: 2/75 p value: 0.276	
								Bilateral calf DVT Confirmed by duplex ultrasonography	Int: 1/75 Control: 1/75 p value: 1	
								Major postoperative	Int: 2/75 Control: 1/75 p	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				factors: not reported				bleeding complications	value: 0.57	
								Length of stay	Int: 6.07 +3.56 days Control: 5.75 +3.24 days p value: 0.566	
								Mortality	Int: 0/75 Control: 0/75 p value: not sig	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Macdonald 2003[211]	RCT	1+	Total: 100 Intervention : n = 51 Control: n = 49	Type of surgery: Patients undergoing craniotomy for brain neoplasm, including trans-sphenoidal surgery, intracranial aneurysm, vascular malformation,	Type: LMWH (Dalteparin) Dose: 2500 IU once per day Timing: Begun at time of surgery and continued for 1 week Additional non-	Type: UFH, low dose Dose: 5000 IU twice per day Timing: Begun at time of surgery and continued for 1 week	1 month	DVT Confirmed by: Doppler US (on 7th post-op day?)	Int: 2/51 Control: 0/49 p value: 0.30	Comments: Excluded patients with VTE, thrombocytopenia, abnormal prothrombin time, abnormal partial thromboplastin time, abnormal bleeding time,
								Symptomatic pulmonary embolism confirmed by ventilation perfusion scan or spiral CT.	Int: 0/51 Control: 0/49 p value: not sig	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				infection, spontaneous intracranial hematoma, closed head injury or cortical resection for epilepsy. Age & Gender: Intervention: Mean age: 51 ±15 yrs M/F:23/28 Control: Mean age: 49 ±15 yrs M/F: 23/26	comparative prophylaxis: Thigh length intermittent pneumatic compression devices worn from time of admission until discharge or the patient was ambulatory for more than 3 hours per day.	Additional non-comparative prophylaxis: Thigh length intermittent pneumatic compression devices worn from time of admission until discharge or the patient was ambulatory for more than 3 hours per day.		Intracranial haemorrhage confirmed by CT scan and MRI	Int: 2/51 Control: 1/49 p value: 0.59	history of hypersensitivity to heparin or pork products, penetrating head injury or pregnancy. Not reported: Proximal DVT, PTS, QoL, LoS Also reported: anaesthesia time; blood loss; no. of patients requiring intraoperative transfusion, surgeon's impression of haemostasis, no. of patients requiring erythrocyte transfusion
								Thrombo-cytopenia	Int: 2/51 Control: 0/49 p value: 0.30	
								Mortality	Int: 0/51 Control: 1/49 p value: 0.48	

Study	Sobieraj-teague 2012[297]
Study type	RCT (Patient randomised; Parallel)

Study	Sobieraj-teague 2012[297]
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Canada; Setting: Hamilton General Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7-11 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People who are contraindicated for pharmacological prophylaxis:
Subgroup analysis within study	Not applicable
Inclusion criteria	Neurosurgical patients aged 18 years or older admitted to Hamilton General Hospital for cranial or spinal neurosurgery; neuro-surgical patients admitted with intracranial haemorrhage (sub-arachnoid, intracerebral, or subdural) who had motor deficits but were not undergoing surgery were eligible if consent was obtained within 24 h of hospital admission.
Exclusion criteria	contraindications to the use of mechanical compression devices, including leg ulceration, symptomatic peripheral neuropathy, or peripheral arterial disease; patients who could not undergo venography because of allergy to contrast medium or pre-existing renal impairment (defined as a glomerular filtration rate of < 50 mL min)1)
Recruitment/selection of patients	May 2009 and November 2010
Age, gender and ethnicity	Age - Mean (range): 62 (29-86). Gender (M:F): 90:60. Ethnicity: Not reported
Further population details	1. Active cancer: Active cancer 56.7% (glioma 20%, meningioma 11.3%, carcinoma metastasis 25.3%). 2. BMI: Obese (BMI over 30 kg/m2) intervention 33.3%, control 34.7%. 3. Mobility: Immobile (Intervention 37.3%, control 32%). 4. Renal impairment: No renal impairment (eGFR greater than 30ml/min/1.73m2) (Excluded people with pre-existing renal impairment).
Indirectness of population	Serious indirectness: Intracranial surgery 75.3%, spinal surgery 10.6%, no surgery 7.3%
Interventions	(n=75) Intervention 1: Intermittent pneumatic compression devices - Below knee. Venowave calf compression device, applied to both calves within 4 hours of surgery or within 24 hours of admission to hospital in non-operated patients. Venowave devices were worn continuously (removed for showering only), and their use was continued until the development of symptomatic VTE, patient refusal, or veno-graphic or ultrasound examination. Duration 7-11 days. Concurrent medication/care: Pharmacological prophylaxis given at the discretion of the neurosurgeon (aspirin 5.3%; unfractionated heparin, or low molecular weight heparin 20%) (n=75) Intervention 2: No treatment - Placebo. Placebo. Duration 7-11 days. Concurrent medication/care: Pharmacological prophylaxis given at the discretion of the neurosurgeon (aspirin 9.3%; unfractionated heparin, or low

Study	Sobieraj-teague 2012[297]
	molecular weight heparin 25.3%)
Funding	Study funded by industry (Golden Horseshoe Bioscience Network; Saringer Incorporated)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IPCD BELOW KNEE versus PLACEBO Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome for People who are contraindicated for pharmacological prophylaxis: DVT (symptomatic and asymptomatic): detected by screening venography or compression ultrasound at 7-11 days; Group 1: 3/75, Group 2: 14/75; Risk of bias: --; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome for People who are contraindicated for pharmacological prophylaxis: PE (symptomatic). confirmed by computed tomography pulmonary angiography at 7-11 days; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study

H.30 Spinal injury

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Green	Patient group: Trauma, complete motor	Group 1	All-cause mortality	Group1: 2/21	Funding:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
1990[128] Country of study: USA Study design: RCT List who was masked to interventions: unclear Evidence level: 1+ Duration of follow-up: 8 weeks	paralysis after spinal cord injury Setting: A regional spinal cord injury care centre in US Inclusion criteria: Complete motor and spinal surgery sustained within the preceding 72 hours Exclusion criteria: Bleeding injuries not accessible to haemostatic control Severe trauma to the head or lower extremities as well as spinal column Coagulopathy or evidence of thrombosis at baseline examination Pregnancy Cardiovascular instability Refusal by patient or next of kin to give informed, written consent All patients N: 41 2 patients in each group failed to complete the planned 8 week trial, because they were transferred 4-29 days after initiation of therapy to other institutions. None of these patients experienced bleeding or thrombosis	Heparin 5000unit, 8 hourly, subcutaneous. Group 2 logiparin (tinzaparin) 3500anti-Xa, subcutaneously, once daily Start time: at least 24 hours after injury. If patient require surgery, morning dose of either heparin or LMWH was withheld, and treatment resumed the following morning End time not explicitly stated. Patients on heparin received drugs for an	(confirmed by:)	Group 2: 0/20 P value: 0.49 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	National Institute of Disability and Rehabilitation Research, Department of Education. Novo Lab supplied logiparin. Limitations: Unmasked: different dosing regimen Duration of prophylaxis not stated a priori, criteria for discontinuation not stated. Haematoma, melaena and haematuria were considered bleeding events if they necessitated the discontinuation of prophylactic therapy and decisions made by ward physicians not participating in the study. Unclear if they were blinded to the study. 2 patients from each arm transferred out – not stated whether analysis based on
			Fatal pulmonary embolism (confirmed by: autopsy)	Group1: 2/21 Group 2: 0/20 P value: 0.49 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	
			Symptomatic DVT (confirmed by: abnormal flow study)	Group1: 1/21 Group 2: 0/20 P value: 1.0 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	
			DVT, asymptomatic or symptomatic (confirmed by: 2 patients confirmed by venography, 3rd patients confirmed by symptom and abnormal flow study. Patients screened with impedence plethysomography, Doppler flow measurement and DUS twice weekly in the first 2 weeks, once	Group1: 3/21 Group 2: 0/20 P value reported: 0.02 (Kaplan Meier Log rank test.) P value: 0.23 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 No. randomised: 21 No. of dropouts: 2 Age (mean): 31.4±15.5 M/F: 17/4 Additional risk factors: Spinal injury location: Cervical:13 Thoracic:6 Lumbar:2 Baseline activate thromboplastin time, aPTT (s): 28.0±2.5 Group 2 No. randomised: 20 No. of dropouts: 4 Age (mean): 28.3±11.8 M/F: 17/3 Additional risk factors: Spinal injury location: Cervical: 10 Thoracic: 9 Lumbar: 1 Baseline activate thromboplastin time, aPTT(s): 27.7±3.3	average of 40±19 days (total of 843 days for 21 patients). Patients on LMWH received drugs for an average of 47±16 days (total of 945 days for 20 patients). Additional non-comparative prophylaxis: Other prophylactic measures such as calf-compression boots, AES and aspirin were withheld.	weekly for the next two weeks, and biweekly for the next 4 weeks)		randomised patient. Outcomes not reported: Symptomatic PE, PE asymptomatic or symptomatic, Calf DVT , Heparin induced thrombocytopaenia, PTS, Pulmonary hypertension, QoL Additional outcomes reported: aPTT for bleeding and thrombotic events Patients on LMWH had more venous studies completed, and more days on prophylaxis. Notes: Study did not report exclusion criteria based on age. Uncertain whether children/teenagers were included 2 patients in LMWH temporarily switched to heparin at Day 22 and Day 23 because LMWH was temporarily not
			Thigh DVT (confirmed by: see DVT. 1 patient; superficial femoral vein, 1 patient popliteal vein, patient had both femoral and popliteal vein)	Group1: 3/21 Group 2: 0/20 P value: 0.23 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	
			Fatal bleeding (description:)	Group1: 0/21 Group 2: 0/20 P value: 1.0 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	
			Upper GI bleeding	Group1: 1/ 21 Group 2: 0/ 0 P value: NS	
			Minor bleeding (description: " 2 patients had bleeding severe enough to require discontinuation of heparin therapy; in both the aPTT was considerably prolonged" Patient 1: neck hematoma, aPTT:	Group1: 2/21 Group 2: 0/20 P value: 0.49 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			44.5s Patient 2: gastrointestinal and genitourinary bleeding, aPTT: 38.0		available
			Length of stay	Group1: 40±19 days Group 2: 47±16 days P value: not reported	

Study	Halim 2014[134]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=74)
Countries and setting	Conducted in India; Setting: Indian Spinal Injuries Centre
Line of therapy	Not applicable
Duration of study	2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with acute spinal cord injury (≤5 days)
Exclusion criteria	Previous history of DVT; chronic venous insufficiency; recent myocardial infarction; heart failure; taking oral contraceptive pills, steroids or hormonal or anticoagulant drugs
Recruitment/selection of patients	December 2006 - December 2010
Age, gender and ethnicity	Age: not reported. Gender (M:F): 60:14. Ethnicity: Indian
Further population details	1. Active cancer: Not applicable (not stated). 2. BMI : Not applicable(not stated). 3. Renal impairment: Not applicable(not stated).
Indirectness of population	No indirectness

Interventions	(n=37) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). LMWH, standard dose (enoxaparin 40mg 1x daily), started on day of admission and continued for 8 weeks. Duration 8 weeks. Concurrent medication/care: mechanical prophylaxis such as AES (n=37) Intervention 2: No treatment - Usual care. No pharmacological VTE prophylaxis. Duration 8 weeks. Concurrent medication/care: mechanical prophylaxis such as AES
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT: confirmed by colour Doppler venous ultrasonography at 12-16 days; Group 1: 2/37, Group 2: 8/37; Risk of bias: --; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE: symptomatic, identified by clinical assessment at 12-16 days; Group 1: 0/37, Group 2: 0/37; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Fatal PE: symptomatic, identified by clinical assessment at 12-16 days; Group 1: 0/37, Group 2: 0/37; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT symptomatic at 12-16 days; Group 1: 2/37, Group 2: 2/37; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Merli 1988[223] Country of study: USA Study design: RCT List who was masked to interventions: investigators & patients blinded to heparin and placebo but not electrical stimulation Evidence level: 1+ Duration of follow-up: at least 28 days, study aim was for 42 days	Patient group: Acute spinal cord injury Setting: Hospital Inclusion criteria: >15 years old injured <2 weeks before initial evaluation classified as having either motor complete or incomplete-preserved motor, non-functional (C2 to T11) lesions Exclusion criteria: underlying bleeding disorder myocardial infarction <6 months long bone fractures arterial trauma post-phlebitic syndrome lower extremity cellulitis hepatic or renal function twice normal pregnant receiving anticoagulant drugs All patients N: 53 * No. of dropouts: 5 Group I	Group I Unfractionated Heparin Start: Unclear Duration: 28 days Dose and Frequency: 5000 IU every 8 hours Group II placebo * 3rd group in trial of UFH + electrical stimulation not reported in this table 88 patients evaluated for the study, 34 excluded because of venographically proven DVT before randomisation. Additional non-comparative prophylaxis:	DVT (asymptomatic & symptomatic) (diagnosed by fibrinogen uptake test confirmed by venography. All patients who had normal fibrinogen uptake tests were also screened with bilateral venography to rule out DVT)	Group 1: 8/16 Group 2: 8/17 P value: not significant	Funding: Regional Spinal Cord Injury Centre of Delaware Valley Model SCI Systems grant from National Institute for Disability Research and Rehabilitation Limitations Treatment reduced from 42 to 28 days once found patients being discharged earlier. Unclear how many received 42 days treatment. Outcomes not reported: pulmonary embolism, DVT, major and minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life, length of stay Additional

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 19 No. of dropouts: 3 Age (mean): NR M/F: NR Additional risk factors: NR Other factors: Group II No. randomised: 17 No. of dropouts: 0 Age (mean): NR M/F: NR Additional risk factors: NR Other factors:	None reported			outcomes reported: Notes: Study terminated early as investigators in review board concerned about ethics of continuing a trial with 3 groups as 3rd group (UFH + electrical stimulation) significantly better than UFH or placebo.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Spinal Cord Injury Thromboprophylaxis Investigators 2003[302] Country of study: Multi-centre	Patient group: Spinal Cord Injury (SCI) Setting: Acute SCI treatment unit Inclusion criteria: Age 15 or older Sustained traumatic SCI from spinal cord level C2 to T12 within previous	Group 1 Low Dose Heparin 5000 U subcutaneously every 8 hours + various IPCD to be used at least 22 hours/day Start time: within 72 hours of injury	All-cause mortality (confirmed by: NR)	Group1: 2/246 Group 2: 2/230 P value:	Funding: Rhone-Poulenc Rorer/Aventis Pharmaceuticals manufacturers of enoxaparin Limitations: Over 3/4 of patients randomised were excluded from

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
study in 27 sites across US & Canada Study design: RCT List who was masked to interventions: Investigators blinded Evidence level: 1+ Duration of follow-up: 8 weeks	72 hours American Spinal Injury Association (ASIA) classification of A (complete motor or sensory deficit) or B (complete motor and incomplete sensory deficit) or C (incomplete motor deficit and sensory deficit with > half muscles having strength grade <3) Exclusion criteria: Objective evidence of bleeding around spinal cord Intracranial bleeding Uncontrolled bleeding at other sites or coagulopathy GI bleeding within previous 2 weeks Pregnancy Conditions precluding use of bilateral IPCD, lower extremity ultrasound or contrast venography Allergy to sulphating agents, heparin or contrast media Uncontrolled hypertension Serum creatinase >2 mg/dL Requirement for anticoagulation as treatment Spinal cord surgery planned for 2 weeks after injury Planned use of aspirin or NSAIDs All patients	Duration: 2 weeks Group 2 LMWH Enoxaparin 30 mg subcutaneously every 12 hours Start time: within 72 hours of injury Duration: 2 weeks Additional non-comparative prophylaxis: Not Applicable			efficacy analysis because they either failed to receive adequate proximal and distal imaging, or discontinued study due to bleeding or platelet counts <100 x 109/L .Data collected for 107 (22.5%) patients remaining were reported with similar baseline characteristics. Outcomes not reported: Symptomatic PE Thigh DVT, Calf DVT Fatal bleeding, Neurological Bleeding Upper GI bleeding, HIT, Post thrombotic syndrome, Pulmonary hypertension Quality of life, Length of Stay Additional

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 476 Age (mean): 36.9 M/F: 389/87 Additional risk factors: BMI: 25.3 ± 4.9 Previous VTE: 3/476 Active Cancer: 3/476 Tetraplegia: 277/476 Paraplegia: 140/476 Group 1 No. randomised: 246 No. of dropouts: 2 patients died during treatment phase. 9 discontinued due to bleeding. Dropouts due to other reasons NR Group 2 No. randomised: 230 No. of dropouts: 2 patients died during treatment phase. 6 discontinued due to bleeding. Dropouts due to other reasons NR				outcomes reported: Discontinuations due to bleeding Group 1: 9/246 Group 2: 6/230 Proximal DVT Group 1: 6/92 (7%) Group 2: 8/89 (9%) Notes: Randomisation by use of sequential sealed envelopes containing computer generated allocations

H.31 Major trauma

Study	Anglen 1998[8]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)

Study	Anglen 1998[8]
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 14 days
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: IPCD group: 38 (17-82), FID group: 41 (18-88)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All adult trauma patients with a fracture of the pelvic ring, acetabulum, or femur were considered for inclusion in the study
Exclusion criteria	Inability to give informed consent, pre-existing thrombosis or active anticoagulation, or the inability to be randomised because at least one of the devices could not be used
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): IPCD group 41 (18-88), foot pump group 38 (17-82): . Gender (M:F): 65:52. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. BMI : Not applicable 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=72) Intervention 1: Intermittent pneumatic compression devices - Below knee. Knee length IPCD placed on the calf of both legs instituted after surgery or in the case of significant preoperative delay, before surgery. Duration Not stated. Concurrent medication/care: All other aspects of care, including pain medication, therapy, use of continuous passive motion, and mobilisation of the patients were the same for the two groups and were dictated by the treating physicians (n=52) Intervention 2: Foot pumps or foot impulse devices - Foot pumps. NuTech Plexipulse foot pumps were placed on both feet. Duration Not stated. Concurrent medication/care: All other aspects of care, including pain medication, therapy, use of continuous passive motion, and mobilisation of the patients were the same for the two groups and were dictated by the treating physicians
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus FOOT PUMPS	

Study	Anglen 1998[8]
Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 14 days; Group 1: 0/68, Group 2: 3/49; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 2 months; Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Dennis 1993[81]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=395)
Countries and setting	Conducted in USA; Setting: Level 1 trauma centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Up to 125 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ISS >9
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	ISS of 9 or less, aged less than 18 years

Study	Dennis 1993[81]
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Prophylaxis groups: 28.6, Control: 27.4. SD not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. BMI : Not applicable 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=189) Intervention 1: Intermittent pneumatic compression devices - Full leg. Full-length lower extremity sequential compression device. Duration Not reported. Concurrent medication/care: Not reported (n=92) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U twice daily. Duration Not reported. Concurrent medication/care: Not reported (n=114) Intervention 3: No treatment - Usual care. No VTE prophylaxis. Duration Not reported. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FULL LEG versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Not reported; Group 1: 2/189, Group 2: 1/92; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at Not reported; Group 1: 5/189, Group 2: 3/92; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Not reported; Group 1: 0/189, Group 2: 0/92; Risk of bias: Very high; Indirectness of outcome: Serious indirectness

Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at Not reported; Group 1: 1/189, Group 2: 1/92; Risk of bias: Very high; Indirectness of outcome: No indirectness

Study	Dennis 1993[81]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FULL LEG versus USUAL CARE Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at Not reported; Group 1: 2/189, Group 2: 4/114; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 5/189, Group 2: 10/114; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 0/189, Group 2: 1/114; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at Not reported; Group 1: 1/189, Group 2: 1/114; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at Not reported; Group 1: 1/92, Group 2: 4/114; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 3/92, Group 2: 10/114; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 0/92, Group 2: 1/114; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at Not reported; Group 1: 1/92, Group 2: 1/114; Risk of bias: Very high; Indirectness of outcome: No indirectness	

Study	Dennis 1993[81]
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Elliott 1999[90]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=149)
Countries and setting	Conducted in USA; Setting: Shock Trauma-Respiratory Intensive Care Unit
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8 days
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: ISS not included as inclusion criteria
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: stratified by presence or absence of femoral venous catheters
Inclusion criteria	Patients who were more than 13 years old with recent (within 24 hours) severe head injury (Glasgow Coma Scale score <9) and/or major trauma and were expected to be bedridden for more than 72 hours
Exclusion criteria	Patients with external fixation devices or casts that precluded the use of calf-thigh sequential pneumatic compression devices on either or both legs, patients who were not expected to live more than 24 hours, and patients in whose injuries occurred more than 24 hours before admission to the unit
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): IPCD group: 33.9 (19.7), FID group: 30.2 (16.0). Gender (M:F): 100:49. Ethnicity: NR
Further population details	1. Active cancer: 2. BMI : 3. Renal impairment:
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Intermittent pneumatic compression devices - Full leg. Calf-thigh sequential pneumatic compression device (Kendall, SCD Compression System, Mansfield, Mass), consisting of four calf and two thigh plastic chambers that inflate sequentially to a pressure of 45mm HG . Duration 8 days . Concurrent medication/care: No AES

Study	Elliott 1999[90]
	or dextran, demopressin acetate, heparin, oral anticoagulants, fibrinolytic agents, dipridimole, or aspirin were permitted (n=75) Intervention 2: Foot pumps or foot impulse devices - Foot pumps. Plantar venous intermittent pneumatic compression device (PlexipulseR, NuTech, San Antonio, Tex), with a single chamber that inflates for 2 seconds and cycles every 20 seconds. The chamber pressure was set to 160mm Hg. Duration 8 days. Concurrent medication/care: No AES or dextran, demopressin acetate, heparin, oral anticoagulants, fibrinolytic agents, dipridimole, or aspirin were permitted
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FULL LEG versus FOOT PUMPS Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at time point not reported; Group 1: 6/74, Group 2: 5/75; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 8 days; Group 1: 4/62, Group 2: 13/62; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 8 days; Group 1: 0/62, Group 2: 0/62; Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Fuchs 2005[109]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=227)
Countries and setting	Conducted in Germany; Setting: Not stated
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients between 18 and 80 years old, had suffered bony or ligamentous trauma to the spine, the pelvis including the acetabulum or the femur, tibia, or ankle. Those who had total hip replacement following a fracture of the femoral neck were also included.
Exclusion criteria	Patients with multiple trauma, had evidence of decompensated coronary heart disease, advanced peripheral arterial occulsion, severe liver failure, haemorrhagic diathesis, stroke, pregnancy, malignant neoplasia, arthritis and arthrodesis of the lower limb, manifest acute thrombosis or thrombophlebitis, pulmonary embolism, paraplegia, chronic muscular dystrophy, and lack of compliance
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Continual motion group: 47.1 (19.7), UFH alone group: 51.9 (19.5). Gender (M:F): 131:96. Ethnicity: NR
Further population details	1. Active cancer: 2. BMI : 3. Renal impairment:
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Continuous passive motion. Passive exercises with Arthroflow device, three times daily for 30 minutes + UFH 5000U three times daily. Duration Not reported . Concurrent medication/care: AES were not used. All patients had intense physiotherapy including breathing exercises, isometric muscle contraction, kinetotherapy, and early mobilisation (n=116) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH 5000U 3 times daily. Duration Not reported. Concurrent medication/care: AES were not used. All patients had intense physiotherapy including breathing exercises, isometric muscle contraction, kinetotherapy, and early mobilisation

Study	Fuchs 2005[109]
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONTINUOUS PASSIVE MOTION + UFH versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 3 months; Group 1: 0/111, Group 2: 0/116; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 3 months; Group 1: 4/111, Group 2: 29/116; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 3 months; Group 1: 0/111, Group 2: 0/116; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Geerts 1996 218	Patient group: Major trauma patients, adult	Group 1 heparin calcium,	All-cause mortality	Group1: 0/173 Group 2: 2/171	Funding: Ontario Ministry of

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: Canada Study design: RCT, double blinded, patients stratified according to the presence or absence of lower extremity fractured List who was masked to interventions: Patients and investigators Evidence level: 1++	Setting: Level I trauma facility in Canada Inclusion criteria: Consecutive adult trauma patients admitted to the trauma centre, who did not have any of the exclusion criteria Exclusion criteria: Any of the following Injury severity score (ISS) <9 Likely to survive or remain in hospital for <7 days Frank intracranial bleeding on computed tomographic scans (cerebral contusion, localized petechial haemorrhages, or diffuse axogonal damage were not excluded) Bleeding that remained uncontrolled 36 hours after the injury Systemic coagulopathy; prothrombin time (PTT) >3s above control value Platelet count <50,000/mm3 Needed therapeutic anticoagulation	5000u, 12hourly. Group 2 Enoxaparin (Clexane), 30 mg For both groups: Given as 0.3-ml subcutaneous injections every 12 hours in a blinded fashion with preloaded syringes. Start: within 36 hours of the injury Duration: up to 14 days. Additional non-comparative prophylaxis: No mechanical or other pharmacologic methods of antithrombotic		P value: 0.25 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	Health, Rhone Poulenc Rorer provided study medications, Mallinckrodt Medical Inc. provided contrast agent for venography Limitations: -Single site study -Method of randomisation concealment not well described Outcomes not reported: Upper GI bleeding QoL, Pulmonary hypertension Additional outcomes reported: Blood transfusions: Heparin: 99/173, 3.8±2.6 units Enoxaparin: 101/171, 4.2±3.1 units Marder Scores:
			Fatal pulmonary embolism (confirmed by: autopsy)	Group1: 0/173 Group 2: 0/171 P value: 1.00 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	
			Symptomatic pulmonary embolism (Confirmed by: ventilation perfusion scan in patients with clinical presentation. Patients with non-diagnostic scans underwent pulmonary angiography, venous ultrasonography, contrast venography, or a combination of these, if necessary, within 24 hours after the scanning)	Group1: 0/136 Group 2: 1/129 P value: 0.49 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Duration of follow-up: Up to 14 days	Cannot undergo venography (allergy to contrast material) renal failure (defined as a serum creatinine level higher than 3.4 mg per decilitre [300 µmol per litter]) pregnant venous access could not be achieved because of amputation or a major foot injury All patients N: 344 No of dropouts: 13 No of patients with sufficient venography: 265 (77%) M/F: 192/265* 99/136 group 1, 93/129 Group2 Group 1 No. randomised: 173 No. of dropouts: 7 Additional risk factors*: - Age (year): 37.0±16.5 - ISS: 22.7±9.0 Predicted risk of DVT†: 54.7±26.3 Surgery performed: 119/136, Blood transfusion in the first 24 hours: 48/136, Maximal mobility (mean of daily corrected score): 2.4±1.0	prophylaxis were allowed by the protocol The study drug was generally not withheld in the event of a surgical procedure, although in exceptional circumstances such as spinal fixation, a single preoperative dose was permitted to be withheld. Treatment with the study medication was then resumed at the first dosing time after the operation.	DVT, asymptomatic or symptomatic (confirmed by: venography of both legs with ioversol, a non-ionic contrast agent between Day 10 and 14, or just before discharged if it occurred earlier. DVT was defined as a constant intraluminal filling defect in a deep leg vein that was seen on ≥2. See above for symptomatic DVT))	Group1: 60/136 Group 2: 40/129 P value: 0.014 (reported) [P=0.03, calculated by NCC-AC team from numbers randomised using Fishers exact test]	Heparin (n=136): 2.3±5.0 Enoxaparin (n=129): 1.0±2.8 (P value: 0.012 by Wilcoxan rank sum test provided by report) Notes: Out of 1076 admissions into the unit, 698 (64.9%) were not eligible The neurological bleeding cases were included in major bleeding.
		Thigh DVT (confirmed by: Proximal-vein thrombosis was defined as thrombosis involving the popliteal or more proximal veins.)	Group1: 20/136 Group 2: 8/129 P value: 0.012 [P=0.03, calculated by NCC-AC team from numbers randomised using Fishers exact test]	
		Calf DVT (confirmed by: see DVT)	Group1: 40/136 Group 2: 32/129 P value: 0.27 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	
		Fatal bleeding (description: confirmed by autopsy)	Group1: 0/173 Group 2: 0/171 P value: 1.0	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Hospital stay (days): 23.5±13.8 Site of major injury: Head: 6/136 Face, chest, abdomen: 53/136 Spine: 24/136 Lower limb (orthopaedic injury): 75/136 Group 2 No. randomised: 171 No. of dropouts: 6 Additional risk factors*: - Age (year): 39.1±16.8 - ISS: 23.1±8.3 Predicted risk of DVT†: 53.5±25.4 Surgery performed: 107/129 Blood transfusion in the first 24 hours: 55/129 Maximal mobility (mean of daily corrected score): 22.4±1.0 Hospital stay (days): 26.0± 15.4 Site of major injury: Head: 7/129 Face, chest, abdomen: 47/129 Spine: 16/129 Lower limb (orthopaedic injury): 69/129 * Information based on patients with adequate venography (n=265) †Predicted risk of thrombosis was		Major bleeding (description: Sites: chest tube, 1000ml of epistaxis, intraoperative, subdural haematoma, facial soft tissues, retroperitoneum)	Group1: 1/173 Group 2: 5/ 171 P value: 0.12 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	
			Neurological bleeding (Subdural haematoma with hemiparesis 4 days after craniotomy for severe skull fracture)	Group1: 0/ 173 Group 2: 1/171 P value: 0.50 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	
			Heparin induced thrombocytopenia (confirmed by heparin-dependent IgG antibodies)	Group1: 2/173 Group 2: 0/ 171 P value: 0.50 [calculated by NCC-AC team from numbers randomised using Fishers exact test]	
			Length of stay	Group1: 23.5±13.8 Group 2: 26.0± 15.4 P value:	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	calculated using this formula: $e^x / 1+e^x$				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ginzburg 2003 222 Country of study: USA Study design: RCT List who was masked to	Patient group: High risk trauma patients with injury severity score >9 259/422 ISS 9-19 148/422 ISS >19 Setting: Trauma centre Inclusion criteria: ■ At least one leg and one arm available for IPCD	Group 1 IPCD (Huntleigh Flowtron). Start time: within 24hrs of trauma End time: until walking independently or discharge from hospital Duration: Maximum disuse	All-cause mortality (confirmed by:)	Group1: 0/224 Group 2: 0/218 P value: NR	Funding: Partly funded by Huntleigh Flowtron. Limitations: Statistics analysis changed part way through due to low incidence of DVT identified.
			Fatal pulmonary embolism (confirmed by:)	Group1: 0/224 Group 2: 0/218 P value: NR	
			Symptomatic pulmonary embolism (confirmed by: clinical suspicion verified by spiral computed tomography or ventilation-perfusion scintigraphy)	Group1: 1/224 Group 2: 1/218 P value: Not significant.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
interventions: No one Evidence level: 1+ Duration of follow- up: 30 days or until discharge from hospital.	No need systemic anticoagulation No contraindications to LMWH Exclusion criteria: <18‟s ISS <9 Patients who were unlikely to survive for at least 7 days Renal failure Pregnant patients Patients unable to undergo Doppler US screening Patients with BMI>25kg/m2 Patients with contraindication to anticoagulation, e.g. intracranial bleeding or uncontrolled haemorrhage. All patients N: 422 Age (mean): Group: 1- 40 Group 2 - 42 M/F: 337:115 Additional risk factors: MI: 12 CHF: 7 COPD:8 Obesity: 7 Cancer: 6 Group 1 No. randomised: 224 No. of dropouts: 15	allowed– 8 hours consecutively Length: calf length (DVT10), compression: 40mmHg on a 60s cycle. First sleeve inflate 12 secs, deflate 48s then repeated in second sleeve. Group 2 LMWH (enoxaparin) Start time: within 24 hrs of trauma End time: until walking independently or discharge from hospital Duration: Dose and frequency: 30mg subcutaneously every 12hrs. Withheld 12hrs before any surgical intervention (max 2 doses missed).	DVT, asymptomatic or symptomatic (screened for by: Doppler ultrasonography weekly and when DVT was suspected.)	Group1: 6/224 Group 2: 1/218 P value: 0.122 Break down is provided for severity USS 9- 19: Gp 1: 4 Gp2: 1 USS >19: Gp 1: 2 Gp2: 0	Intention to treat analysis not completed. Outcomes not reported: Asymptomatic PE, location of DVT, HIT, PTS, Pulmonary hypertension, QoL Notes: Where patients could not use leg for IPCD – it was placed on arm. 2 DVTs occurred in patients with IPCD on one leg and one arm. Subgroups by injury severity. Some patients underwent surgery during the study but there is no indication of
			Fatal bleeding (description:)	Group1: 0/224 Group 2: 0/218 P value: NR	
			Major bleeding (description: haemorrhage leading to a fall in haemoglobin conc. of 2 g/dl, transfusion of 2 or more of packed red blood cells, intracranial or retroperitoneal bleeding or bleeding requiring surgical intervention)	Group1: 4/224 Group 2: 4/218 P value: NR	
			Minor bleeding (description: excessive bleeding from operative sites, gastrointestinal bleeding and/ or haematuria that did not meet the criteria for major bleeding)	Group1: 4/224 Group 2: 9/218 P value: 0.245	
			Length of stay	Group1: 20.9 (33.4) Group 2: 15.5 (15.0) P value: 0.040	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 No. randomised: 218 No. of dropouts: 29	Additional non-comparative prophylaxis: None			how many and in which groups.

Study	Knudson 1994[173]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=251)
Countries and setting	Conducted in USA; Setting: Trauma centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: At least 3 weeks
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Knudson 1994[173]
Inclusion criteria	One of the following: laparotomy, thoracotomy, ventilated >24 hours, spine fracture, pelvic fracture, femur fracture
Exclusion criteria	Patients who were younger than 18 years, pregnant or prisoners, and those found to already have DVT on the initial venous imaging study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 38 (18-90). Gender (M:F): 200:51. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. BMI : Not applicable3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Low dose heparin administered subcutaneously every 12 hours. Duration Not reported. Concurrent medication/care: Not reported (n=58) Intervention 2: Intermittent pneumatic compression devices - Full leg. Thigh length sequential gradient pneumatic compression devices and AES. Prophylactic measures were instituted as soon as possible following the screening duplex venous examination and always within 24 hours of admission. Duration Not reported . Concurrent medication/care: Not reported (n=130) Intervention 3: No treatment - Usual care. No treatment group. Duration Not reported . Concurrent medication/care: Not reported
Funding	Study funded by industry (Supported by the Kendall Healthcare Products Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus FULL LEG + AES

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 3 weeks; Group 1: 1/44, Group 2: 4/32; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 3 weeks; Group 1: 0/44, Group 2: 0/32; Risk of bias: ; Indirectness of outcome: No indirectness

Study	Knudson 1994[173]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome for People who are contraindicated for mechanical prophylaxis: All-cause mortality at 3 weeks; Group 1: 0/19, Group 2: 1/27; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 3 weeks; Group 1: 1/44, Group 2: 2/64; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome for People who are contraindicated for mechanical prophylaxis: DVT at 3 weeks; Group 1: 1/19, Group 2: 2/27; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 3 weeks; Group 1: 0/44, Group 2: 1/64; Risk of bias: ; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FULL LEG + AES versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 3 weeks; Group 1: 4/32, Group 2: 2/64; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for People who are contraindicated for pharmacological prophylaxis: DVT at 3 weeks; Group 1: 0/26, Group 2: 5/39; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 3 weeks; Group 1: 0/32, Group 2: 1/64; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days

Study	Knudson 1994[173]
	from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Knudson 1996[174] Country of study: USA Study design: RCT List who was masked to interventions: None Evidence level: 1+ Duration of follow-up: Not reported.	Patient group: Trauma Setting: San Fransisco General Hospital Trauma Center. Inclusion criteria: Patients admitted to trauma centre meeting one or more of the following conditions: Injury Severity Score >10 Abbreviated Injury Scale score >3 in any category (n=316) Head injury with Glasgow Coma Scale <8 (n=42) unstable spine fracture without neurologic deficit (n=16) stable spine fracture with deficit (n=25) major pelvic fracture (n=13) fracture of the lower extremity above the ankle (n=101) age >50 (n=78) Exclusion criteria:	All interventions started within 24 hours of admission. Not stated for how long the study continued. Possibly until discharge or transfer to another unit. Group 1 LMWH (enoxaparin, Rhone Poulnec), 30mg subcutaneously every 12 hours Group 2 bilateral sequential gradient compression devices (SCD) (length not stated) and AES	All-cause mortality	Group1: 0/120 Group 2: 0/82 P value: NA	Funding: Supported by grant from Rhone Poulnec Outcomes not reported: All-cause mortality, symptomatic, calf, thigh and/or proximal DVT, heparin induced thrombocytopenia, post-thrombotic syndrome, bleeding outcomes, pulmonary hypertension, quality of life & length of stay Additional outcomes reported: Bleeding from drain site, reoperation for bleeding, drop in haematocrit, bruise at injection site, non-compliance
			Fatal pulmonary embolism (confirmed by: autopsy)	Group1: 0/120 Group 2: 0/82 P value: NA	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	presence of DVT major neurologic injury (head or spinal) presence of solid organ injury managed non-operatively coagulation abnormalities or active bleeding beyond 36 hours neck hematomas secondary to initial trauma platelet counts <50,000 at 24 hours after injury All patients N: 202 Age (mean): 38.6 years M/F: NR Additional risk factors: NR Group 1 No. randomised: 120 No. of dropouts: 0 Group 2 No. randomised: 82 No. of dropouts: 0	TED (Kendall Healthcare Products) 61/82 OR arteriovenous impulse device (AVI) requiring only a foot pad if unable to wear SCD 21/82 Additional non-comparative prophylaxis: none	Symptomatic pulmonary embolism (confirmed by: ventilation perfusion scan)	Group1: 0/120 Group 2: 0/82 P value: NA	rate, units of blood transfusion Specific details of patients with DVT occurring during study period. Notes: * p values calculated by NCC-AC using Fisher Exact test. The paper also includes a 3rd arm of patients (not reported here) of patients excluded from this randomised part and all assigned to mechanical compression
			DVT, asymptomatic or symptomatic (confirmed by: duplex ultrasonography)	Group1: 1/120 Group 2: 2/82 P value: NR p = 0.57 *	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Length of stay (mean no. of hospital days)	Group1: 12.7 days (n=120) Group 2: 11 days (n=82) P value: not significant	

Study	Kurtoglu 2004[180]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Turkey; Setting: ICU
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 1 week post discharge
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with severe head/spinal injuries
Exclusion criteria	Patients younger than 14 years old, those with hepatic or urinary dysfunction, a spinal cord injury, a history of DVT, or a high bleeding risk, and those using anticoagulants

Study	Kurtoglu 2004[180]
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (range): 37.1 (18-76). Gender (M:F): 47:73. Ethnicity: not reported
Further population details	1. Active cancer: Not applicable2. BMI : Not applicable 3. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Intermittent pneumatic compression devices - Below knee. Below knee IPCD (prophylactic DVT system, model AC 550; Flowtron Excell or AV impulse system, Duo; Novamedix) applied following admission to ICU. Duration Not reported. Concurrent medication/care: Not reported (n=60) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 40mg 1 x daily. Duration Not reported. Concurrent medication/care: All patients received IPCD on admission, andinitiation of LMWH was determined after CT within 24 hours of admission
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at not reported; Group 1: 7/60, Group 2: 8/60; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at not reported; Group 1: 4/60, Group 2: 3/60; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at not reported; Group 1: 0/60, Group 2: 0/60; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at not reported; Group 1: 0/60, Group 2: 0/60; Risk of bias: High; Indirectness of outcome: Serious indirectness

Study	Kurtoglu 2004[180]
Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at not reported; Group 1: 5/60, Group 2: 4/60; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Stannard et al., 2006 620 [US] Study design: RCT List who was masked to interventions:	Patient group: Patients with recent blunt skeletal trauma (i.e. starting at admission) Setting: Hospital admission / ward Inclusion criteria: blunt trauma and at least one of the following –	Group 1 Enoxaparin (30mg administered subcutaneously twice a day) Start time: 24 – 48 hours after blunt trauma once severe bleeding associated with trauma had been	All-cause mortality	Group1: 0/103 Group 2: 0/97 P value: NA	Funding: "In support of their research for or preparation of this manuscript one or more of the authors received grants or outside funding from Aventis Pharmaceutical
			Fatal pulmonary embolism	Group1: 0/103 Group 2: 0/97 P value: NA	
			Symptomatic pulmonary embolism, (not stated how confirmed only states „underwent test" to exclude)	Group1: 0/103 Group 2: 2/97 P value: 1.00 (Not Sig)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
NA Evidence level: 1+ Duration of follow- up: Mean 17 months (range 6 – 38months)	▪An Abbreviated Injury score of 3 or more and a long bone fracture ▪Multiple (2 or more) long bone fractures ▪An age of more than 55 years and a long bone fracture. All patients were 18+ yrs, had no contraindication for anticoagulation and had been admitted to hospital less than 2 hours after time of trauma or had a negative magnetic resonance venogram prior to enrolment. Exclusion criteria: renal insufficiency, severe cranial or spinal cord injury; the use of anticoagulants; any contraindication to anticoagulation, including severe active bleeding; pregnancy; a history of venous thromboembolic disease; any contraindication to magnetic resonance venography; the presence of vena cava filters; and severe ocular trauma. All patients N: 200 Age (mean): 39.6 (range 19-80) M/F: NR	controlled. Anyone not able to start within 72 hours excluded from study. Group 2 Pulsatile foot pumps at time of admission (patients asked to use it for at least 12 hours per day) combined with enoxaparin on a delayed basis (5 days after admission) after all acute bleeding from blunt trauma had been resolved. NB: Prophylaxis was given for duration of hospital stay. If patients required a return to the operating theatre, the enoxaparin was	DVT, asymptomatic or symptomatic (confirmed by: bilateral magnetic resonance venography and ultrasonography within 24 hours before discharge or as soon as they developed signs or symptoms of DVT)	Group1: 9/103 Group 2: 13/97 P value: 0.2365 (Not Sig)	Grant in Aid. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, educational institution, or other charitable or non-profit organisation with which the authors are affiliated or associated". Limitations: unclear how patients were randomised. No intention to treat analysis (10.7% dropout rate). Lack of bleeding data. Outcomes not
			Symptomatic DVT (confirmed by: magnetic resonance venography and ultrasonography within 24 hours before discharge or as soon as they developed signs or symptoms of DVT)	Group1: 1/103 Group 2: 1/97 P value: NS	
			Fatal bleeding	Group1: 0/103 Group 2: 0/97 P value: NA	
			Neurological bleeding	Group 1: 1/103 Group2: 1/97 P value: 0.7362 (Not Sig)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		discontinued on the night prior to surgery and resumed within 12 hours after surgery.			reported: Upper GI bleeding Major bleeding Minor bleeding Heparin induced thrombocytopaenia Post thrombotic syndrome Quality of life Pulmonary hypertension
	Additional risk factors: Injury severity score (mean): 14.42 (range 4-57) Weight (mean): In kgs: 85.7 (range: 45.4 – 158.8) In lbs: 189 (range: 100 – 350) Group 1 No. randomised: 103 No. of dropouts: 0 Age (mean): 41.0(range 19-80) Additional risk factors: Injury severity score (mean): 14.43 (range 4-41) Weight (mean): In kgs: 86.2 (range: 45.4 – 158.8) In lbs: 190 (range: 100 – 350) Group 2		Length of stay	Group 1: 13.8 days (range: 3-68 days) Group2: 11.2 (range: 1-119 days) P value: NR (unable to calculate)	Additional outcomes reported: No. of DVTs that were occlusive (significantly more in Group 1 i.e. 11 compared to 3, p=0.025) Mean number of fractures per patient (by DVT vs. no DVT). % with acetabular fracture for DVT vs no DVT in each group. Mean duration of prophylaxis by DVT development. Mean duration of foot pump use

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 97 No. of dropouts: 0 Age (mean): 38.2(range 19-75) Additional risk factors: Injury severity score (mean): 14.41 (range 8-57) Weight (mean): In kgs: 84.8 (range: 46.3 – 153.3) In lbs: 187 (range: 102 – 338) [NB: 24/224 (10.7%) did not complete the protocol and are excluded from the results, 5 because of erroneous discharge before studies were obtained, 5 because of claustrophobia in MRI scanner, 5 because of bleeding that required discontinuation of anticoagulants, 4 withdrew from the study, 3 had errors in medication and two had other medical problems that required discontinuation of anticoagulants.]				(13.3 hrs per day, range 1-23 hrs) Time of prophylaxis initiation against DVT Mean number of surgical procedures per patient (by DVT vs. no DVT). No. of wound infections, wound hematomas at surgical site and other site, pseudoaneurysm, large hematoma. Prevalence of high risk skeletal injuries

H.32 Abdominal surgery (excluding bariatric surgery)

Study	Agnelli 2005[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2927)
Countries and setting	Conducted in Multiple countries; Setting: Hospital
Line of therapy	--Please Select--
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients due to undergo abdominal surgery expected to last more than 45 minutes and were aged over 60 year, or aged over 40 years with one or more additional risk factors for thromboembolic complications, including obesity (BMI >30 for men and >28.6 for women), a history of venous thromboembolism, congestive obstructive pulmonary disease, inflammatory bowel disease, or surgery for cancer
Exclusion criteria	Patients who were having urological, gynaecological, laparoscopic, vascular or emergency trauma surgery. Also, patients with a life expectancy less than 2 months, active bleeding, a document bleeding disorder or thrombocytopenia, ulcerating or angiodysplastic gastrointestinal disease that was not the reason for surgery, a haemorrhagic stroke or surgery of the brain, spine or eye within the previous 3 months, bacterial endocarditis or another contraindication to anticoagulant therapy, pregnancy, hypersensitivity to contrast media, or a serum creatinine concentration above 180 µmol/l in a well hydrated patient
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): Fondaparinux group: 66 (31-92), LMWH group: 65 (17-93). Gender (M:F): 1584:1274. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed population (67-70% cancer surgery)). 2. Acute/elective: Not applicable 3. BMI : Mixed (22% BMI >30). 4. Laparoscopic/open surgery: Open surgery (Laparoscopic surgery was excluded). 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=1465) Intervention 1: Fondaparinux - Fondaparinux (all doses). Fondaparinux 2.5mg. The first injection was 6 hours after surgical closure. Patients received a placebo injection 2 hours before surgery and again 12 hours later to

	correspond with the LMWH schedule. Duration 5-9 days. Concurrent medication/care: Patients were discouraged from using aspirin, thienopyridines and non-steroidal anti-inflammatory drugs, but the use of AES was permitted and early mobilisation was recommended. Indirectness: No indirectness (n=1462) Intervention 2: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 2500 units given 2 hours before induction of aneasthesia and 12 hours later, then once daily at a dose of 5000 units. Patients receied a placebo injection 6 hours after surgery to correspond with the fondaparinux schedule. Duration 5-9 days. Concurrent medication/care: Patients were discouraged from using aspirin, thienopyridines and non-steroidal anti-inflammatory drugs, but the use of AES was permitted and early mobilisation was recommended. Indirectness: No indirectness
Funding	Study funded by industry (Supported by a grant Sanofi-Synthelabo and NV Organon)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX (ALL DOSES) versus DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 32 days; Group 1: 40/1433, Group 2: 55/1425
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32; Group 2 Number missing: 37

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 32 days; Group 1: 43/1024, Group 2: 59/1018
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 441; Group 2 Number missing: 444

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 32 days; Group 1: 2/1465, Group 2: 0/1462
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening

clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 7-11 days; Group 1: 49/1433, Group 2: 34/1425 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32; Group 2 Number missing: 37 Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 7-11 days; Group 1: 3/1465, Group 2: 3/1462 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Allan 1983[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in United Kingdom; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over the age of 40 years undergoing elective abdominal surgery of at least 30 minutes duration
Exclusion criteria	Patients with a history of previous DVT or PE, or found to have varicose veins or superficial vein thrombosis, or receiving steroid or anticoagulation
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 40-80+. Gender (M:F): 100:100. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (50% had a malignant disease). 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=97) Intervention 1: Anti-embolism stockings - Mixed above/below knee. TED stockings on both legs, fitted the evening before the operation and worn for at least 7 days after. Duration 7 days . Concurrent medication/care: Not stated . Indirectness: No indirectness (n=103) Intervention 2: No treatment - Usual care. Control group did not wear AES. No further details reported . Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Stockings and fibrinogen supplied by Kendall Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED ABOVE/BELOW KNEE versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 7 days; Group 1: 15/97, Group 2: 37/103

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only age and sex reported; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Allen 1978[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in United Kingdom; Setting: Hospital
Line of therapy	1st line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing transurethral prostatectomy
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Average age - UFH group: 71.2, control group: 71.9. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000 units of subcutaneous calcium heparin, administered 2 hours before operation and then 12-hourly until the patient left hospital . Duration Not reported . Concurrent medication/care: Not reported . Indirectness: No indirectness (n=30) Intervention 2: No treatment - Usual care. Control group. No further details given . Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Time-point not reported; Group 1: 0/30, Group 2: 0/30

Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Time-point not reported; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Method of confirmation not reported; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Time-point not reported; Group 1: 6/30, Group 2: 0/30 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Bejjani 1983[18]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=34)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients undergoing transurethral prostatectomy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Patients who had bleeding disorders, a contraindication for anticoagulation, or were on drugs affecting coagulation
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 38% had cancer). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH 5000 units of sodium heparin, started 3 hours preoperatively and every 12 hours thereafter for 48 hours. Duration 2 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=17) Intervention 2: No treatment - Placebo. Placebo. 2ml of normal saline three hours preoperatively and every 12 hours thereafter for 48 hours . Duration 2 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at time-point not reported; Group 1: 0/17, Group 2: 1/17

Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at time-point not reported; Group 1: 1/17, Group 2: 0/17 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Bergqvist 1980[26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=97)
Countries and setting	Conducted in Sweden; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: General and urological surgery (>80% abdominal)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over the age of 50 admitted for elective general and urologic surgery
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): LMWH group: 66.7 (52-89), control group: 66.7 (51-85). Gender (M:F): 66:34. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 22% malignant disease). 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=53) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Low dose heparin in a dose of 5000U injected subcutaneously 2 hours before operation and at 12 hourly intervals for 5 days post operatively. Duration 5 days. Concurrent medication/care: All groups had conventional physiotherapy and early mobilisation according to the department of surgery routine. Indirectness: No indirectness (n=58) Intervention 2: No treatment - Usual care. No specific prophylaxis . Duration 5 days. Concurrent medication/care: All groups had conventional physiotherapy and early mobilisation according to the department of surgery routine. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE	

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 7 days; Group 1: 2/46, Group 2: 7/51 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 7 days; Group 1: 6/46, Group 2: 14/51 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7 Protocol outcome 3: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 7 days; Group 1: 0/46, Group 2: 0/51 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study;

Study	Bergqvist 1986[24]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=432)
Countries and setting	Conducted in Sweden; Setting: Department of surgery
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients undergoing elective general abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged over 40 who were undergoing elective general abdominal surgery of more than 30 minutes duration
Exclusion criteria	Heparin or iodine hypersensitivity, impaired renal function, septic endocarditis, stroke, haemorrhagic diathesis, treatment with anticoagulants, pregnancy
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 45% malignancies). 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairment (eGFR greater than 30ml/min/1.73m2) (Doesn't specify eGFR but says it excludes 'impaired renal function').
Indirectness of population	No indirectness
Interventions	(n=215) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 5000U given 2 hours before surgery and then every morning for 5-7 days. Duration 5-7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=217) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Heparin 5000U given subcutaneously 2 hours before operation and at 12 hour intervals for 5-7 days. Duration 5-7 days. Concurrent medication/care: Not reported . Indirectness: No indirectness
Funding	Academic or government funding (Supported by a grant from the Swedish Medical Research council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 30 days; Group 1: 5/215, Group 2: 5/217 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 30 days; Group 1: 13/215, Group 2: 9/217 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 30 days; Group 1: 20/215, Group 2: 2/217 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Bergqvist 1988[27]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1002)
Countries and setting	Conducted in Sweden; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients undergoing elective abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were 40 years of age or older and scheduled to undergo major elective general abdominal surgery of more than 30 minutes duration with an expected postoperative stay in hospital of at least 5 days
Exclusion criteria	Vascular and urogenital surgery, heparin or iodine hypersensitivity, impaired renal function (creatinine >200µmol/l), septic endocarditis, haemorrhagic stroke, known bleeding diathesis, treatment with oral anticoagulants or dextran within 14 days, pregnancy
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): LMWH group: 68 (41-91), UFH group: 69 (41-91). Gender (M:F): 488:514. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Excludes creatinine >200µmol/l).
Indirectness of population	No indirectness
Interventions	(n=505) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin, 5000U. Patients were given the first injection the evening before surgery, and the second 2 hours before surgery, and then once daily for 5-8 days. Duration 5-8 days. Concurrent medication/care: Not reported . Indirectness: No indirectness (n=497) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U. Patients were given the first injection the evening before surgery, and the second 2 hours before surgery, and then twice daily for 5-8 days. Duration 5-8 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Supported by a grant from the Swedish Medical Research Council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 30 days; Group 1: 10/505, Group 2: 10/497
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 38 patients excluded due to fine reasons but not reported which group they were in; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 30 days; Group 1: 28/505, Group 2: 41/497
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 38 patients excluded due to fine reasons but not reported which group they were in; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 30 days; Group 1: 0/505, Group 2: 4/497
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 38 patients excluded due to fine reasons but not reported which group they were in; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 30 days; Group 1: 0/505, Group 2: 1/497
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 38 patients excluded due to fine reasons but not reported which group they were in; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge;

Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;	

Study	Bergqvist 1995[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2070)
Countries and setting	Conducted in Sweden; Setting: One of 7 centres
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients having elective general abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients above 40 years of age undergoing elective general abdominal surgery lasting at least 30 minutes and with an expected postoperative stay of at least 5 days
Exclusion criteria	Vascular, thoracic, thyroid and urogenital operations, heparin or iodine hypersensitivity, serum creatinine level above 200µmol/l, septic endocarditis, haemorrhagic stroke, bleeding diathesis, treatment with anticoagulants or dextran within 14 days, pregnancy; and previous inclusion in the trial
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): low dose group: 69 (40-95), standard dose group: 70 (40-90). Gender (M:F): 985:1085. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Serum creatinine level above 200µmol/l was excluded).
Indirectness of population	No indirectness
Interventions	(n=1034) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin 2500U, once daily. First does given subcutaneously the evening before surgery and repeated daily. Duration 7 days. Concurrent medication/care: Dextran or additional heparin was now allowed. Indirectness: No indirectness (n=1036) Intervention 2: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin 5000U, once daily. First does given subcutaneously the evening before surgery and repeated daily. Duration 7 days. Concurrent medication/care: Dextran or additional heparin was now allowed. Indirectness: No indirectness

Funding	Academic or government funding (Supported by Swedish Medical Research Council grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN LOW DOSE (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus DALTEPARIN STANDARD DOSE (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 30 days; Group 1: 35/1034, Group 2: 32/1036
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 30 days; Group 1: 124/976, Group 2: 65/981
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 58; Group 2 Number missing: 55

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 30 days; Group 1: 4/976, Group 2: 6/981
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 58; Group 2 Number missing: 55

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 30 days; Group 1: 3/1034, Group 2: 13/1036
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Bergqvist 1996[25]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Sweden; Setting: Three centre's
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People undergoing emergency general abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients above 40 years of age if they underwent emergency general abdominal surgery within 48 hours from admission with an expected operation time of more than 30 minutes and an estimates hospital stay of 5 days or more
Exclusion criteria	Preoperative treatment with heparin, acute re-operation, serum creatinine >200µmol/l, hepatic failure, childbearing potential, head injury or multitrauma, allergy to iodine or heparin, treatment with oral anticoagulants or fibrinolytic agents or inability to give informed consent
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): LMWH group: 69 (41-87), placebo group: 71 (43-92). Gender (M:F): 37:43. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed - 13.8% malignant disease). 2. Acute/elective: Acute 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Excluded serum creatinine >200µmol/).
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Low molecular weight heparin (licensed in UK) - Tinzaparin (2,500 units once daily – 9,000 units once daily). 3500U tinzaparin, started postoperatively, given once daily. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=41) Intervention 2: No treatment - Placebo. Placebo (0.9% saline) once daily. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TINZAPARIN (2,500 UNITS ONCE DAILY – 9,000 UNITS ONCE DAILY) versus PLACEBO	

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 30 days; Group 1: 0/39, Group 2: 2/41 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 30 days; Group 1: 3/39, Group 2: 9/41 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 30 days; Group 1: 0/39, Group 2: 1/41 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 30 days; Group 1: 1/39, Group 2: 0/41 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Borstad 1988[32]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=215)
Countries and setting	Conducted in Norway; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients having major gynaecological surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 40 years or more, undergoing major gynecological surgery lasting more than 30 min. Further inclusion criteria were: previous history of thromboembolism or malignancy, estrogen medication for the last 30 days, serious varicose veins or overweight exceeding 20%.
Exclusion criteria	Patients were excluded if they had a known bleeding tendency, a history of CNS bleeding, impaired renal function, hypersensibility to heparin, decreased level of antithrombin, or if they received anticoagulation therapy. Pregnant women and patients having epidural anesthesia were also excluded
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 53.4 (11.6), UFH group: 53.6 (10.4). Gender (M:F): Female. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed - 6%). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Excluded imparied renal function).
Indirectness of population	No indirectness
Interventions	(n=105) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 5000U LMWH (Heparin fragment KABI 2165, KabitVitrum, Sweded) 1 hour preoperatively and then every 24 hours for 7 days. Duration 7 days. Concurrent medication/care: Not reported (n=110) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U UFH (conventional heparin from pig mucosa, KabiVitrum Sweden) subcutaneously every 12 hours. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 7 days; Group 1: 0/105, Group 2: 0/110 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 7 days; Group 1: 0/105, Group 2: 0/110 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 7 days; Group 1: 32/105, Group 2: 13/110 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Borstad 1992[33]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=152)
Countries and setting	Conducted in Norway; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients undergoing major gynecological surgery, laparotomy, vaginal repair or colposuspension
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age over 40 years, previous history of thromboemolism or malignancy, hormone replacement therapy during the last 30 days, serious varicose veins or overweight exceeding 2-%
Exclusion criteria	Hemorrhagic diathesis, known antithrombin deficiency, treated with anticoagulants during the last 14 days, had recent cerebro-vascular hemorrhage or impaired renal function (creatinine >300umol/l), women with hypersensitivity to heparin, pregnant women and those who were going to have epidural anesthesia
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 56.3 (10.4), UFH group: 57.1 (12.7). Gender (M:F): Female. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Excluded impaired renal function (creatinine >300umol/l)).
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 2500U of Fragmin (Kabi Pharmaciam Sweden), 1 hour preoperatively and then every 24 hours for 7 days. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=75) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U of UFH (kabi Pharmacia, Swededn) every 12 hours. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 1 month; Group 1: 2/71, Group 2: 0/70 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: ; Group 2 Number missing: 5 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 1 month; Group 1: 0/71, Group 2: 0/70 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: ; Group 2 Number missing: 5 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 1 month; Group 1: 1/71, Group 2: 0/70 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: ; Group 2 Number missing: 5 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 5 days; Group 1: 14/71, Group 2: 9/70 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: ; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Butson 1981[38]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=119)
Countries and setting	Conducted in Canada; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Up to 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients undergoing abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Only patients undergoing an abdominal surgery procedure of a severity equal to or greater than that of cholecystectomy
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): IPCD group: 52.4 (20-89), control group:57.5 (25-91). Gender (M:F): 52:67. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: Intermittent pneumatic compression devices - Below knee. Inflatable plastic knee length leggings were inflated by compressed air pumps (PED-90, Lyne-Nicholson Inc., Needham Heights, Massachusetts). IPCD was started in the operating room immediately after anesthesia and was continued until the patient was ambulatory, usually 24-48 hours. A few patients were kept on IPCD for up to 4 days. Duration 24-48 hours. Concurrent medication/care: Both groups had routine daily postoperative physiotherapy. Indirectness: No indirectness (n=57) Intervention 2: No treatment - Usual care. Control group. Duration Not reported. Concurrent medication/care: Both groups had routine daily postoperative physiotherapy. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler)

ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 14-90 days; Group 1: 6/62, Group 2: 4/57 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 14-90 days; Group 1: 0/62, Group 2: 1/57 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Caen 1988[39]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=391)
Countries and setting	Conducted in France; Setting: 5 hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients undergoing major abdominal surgery
Stratum	Overall:
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 40 years or above and scheduled to undergo abdominal surgery of a duration of more than 30 minutes under general aneasthesia
Exclusion criteria	Haemorrhagic diathesis, impaired renal function, severe hepatic insufficiency, cerebral haemorrhage within the last 6 months, septic endocarditis, heparin or iodine hypersensitivity, treatment with oral anticoagulants within the last 3 months
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group 52.2 (11.9), UFH group 59.7 (11.8). Gender (M:F): 188:197. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Excluded impaired renal function).
Indirectness of population	No indirectness
Interventions	(n=195) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Kabi 2165 2500U given subcutaneously 2 hours before operation and then every morning for the next 7 postoperative days. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=190) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Low dose standard heparin, 5000U given subcutaneously, 2 hours before operation and at 12 hourly intervals for the next 7 days. Duration 7 days. Concurrent medication/care: Not reported . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED

HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 30 days; Group 1: 2/195, Group 2: 3/190 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 6 patients excluded but not clear which group they were in; Group 2 Number missing: Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 30 days; Group 1: 6/195, Group 2: 7/190 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 6 patients excluded but not clear which group they were in; Group 2 Number missing: Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 30 days; Group 1: 0/195, Group 2: 0/190 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 6 patients excluded but not clear which group they were in; Group 2 Number missing: Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 30 days; Group 1: 0/195, Group 2: 0/190 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 6 patients excluded but not clear which group they were in; Group 2 Number missing:	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	CANBESURE trial: Kakkar 2010[164]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=626)
Countries and setting	Conducted in Multiple countries; Setting: Secondary/Tertiary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Interventions 20 days + Follow-up maximum 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Bilateral venograms were performed on all participants 20 days after randomisation. Suspected DVT were confirmed by unilateral venography or Doppler ultrasound. Non-fatal PE was verified by perfusion/ventilation lung scintigraphy, pulmonary arteriography or spiral computed tomography.
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	Aged 40 years or older admitted to undergo elective, open, curative or palliative surgery for a malignant disease of the gastrointestinal tract (excluding oesophagus), genitourinary tract or female reproductive organs
Exclusion criteria	Active haemorrhage / High risk of bleeding; known hypersensitivity to unfractionated/fractionated heparins, radiological contrast media or anaesthetic drugs; tumour of / surgical intervention in the central nervous system within the previous 6 months; endocarditis; treatment with oral/parenteral anticoagulants within 5 days before surgery; history of heparin-induced thrombocytopenia / baseline platelet count < 75,000µ/L; severe renal/hepatic insufficiency; severe arterial hypertension; VTE within the previous 3 months; inability to comply with the study treatment and/or follow-up; cava filter; receiving prohibited medications; pregnancy/lactation; surgery for liver cancer, biliary tract or pancreas
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Bemiparin 64.1 (10.3) vs. Placebo 64.6 (9.9). Gender (M:F): 330:295. Ethnicity: Caucasian 99.7%; Other 0.3%
Further population details	1. Active cancer: Active cancer (GI tract = 80.6%; Female reproductive organs = 11.4%; Urologic = 7.5%; Retroperitoneal = 0.5%). 2. Acute/elective: Elective (Elective = 100%). 3. BMI : Obese (BMI over 30 kg/m2) (Obesity = 18.6%). 4. Laparoscopic/open surgery: Open surgery (Open = 100%). 5. Renal impairment: Not applicable(Not stated).
Indirectness of population	No indirectness
Interventions	(n=316) Intervention 1: Low molecular weight heparin (not licensed in UK) - Bemiparin (2500 units once daily - 3500 units once daily). Subcutaneous injections of bemiparin 3500IU (0.2ml) once daily . Duration 20 ± 2 days. Concurrent medication/care: Run-in period before randomisation: subcutaneous injections of bemiparin 3500IU (0.2ml) for 8 ± 2 days. Indirectness: Serious indirectness; Indirectness comment: Bemiparin is not licensed in UK

	(n=310) Intervention 2: No treatment - Placebo. Subcutaneous injections of placebo (0.9% NaCl, 0.2ml) once daily . Duration 20 ± 2 days. Concurrent medication/care: Run-in period before randomisation: subcutaneous injections of bemiparin 3500IU (0.2ml) for 8 ± 2 days. Indirectness: No indirectness
Funding	Study funded by industry (Laboratorios Farmacéuticos Rovi S.A.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEMIPARIN versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause death during intervention period at 20 ± 2 days; Group 1: 6/248, Group 2: 3/240; Comments: RRR -93.6 (95% CI -665.1 to 51.0); p=0.50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68, Reason: 1 participant was not treated + Venography not performed for 44 participants + Venography was of poor quality in 18 participants + 5 had unilateral venography; Group 2 Number missing: 70, Reason: Venography not performed for 42 participants + Venography was of poor quality in 17 participants + 11 had unilateral venography
- Actual outcome: All-cause death during intervention and follow-up period at Up to 90 days; Group 1: 8/248, Group 2: 6/240; Comments: RRR -29.0 (95% CI -266.4 to 54.6); p=0.63
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68, Reason: 1 participant was not treated + Venography not performed for 44 participants + Venography was of poor quality in 18 participants + 5 had unilateral venography; Group 2 Number missing: 70, Reason: Venography not performed for 42 participants + Venography was of poor quality in 17 participants + 11 had unilateral venography

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT during intervention period at 20 ± 2 days; Group 1: 19/248, Group 2: 29/240; Comments: RRR 36.6 (95% CI -10.0 to 63.4); p=0.10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68, Reason: 1 participant was not treated + Venography not performed for 44 participants + Venography was of poor quality in 18 participants + 5 had unilateral venography; Group 2 Number missing: 70, Reason: Venography not performed for 42 participants + Venography was of poor quality in 17 participants + 11 had unilateral venography

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding during intervention period at 20 ± 2 days; Group 1: 2/315, Group 2: 1/310
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 participant was not treated; Group 2 Number missing: 0 Protocol outcome 4: Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge - Actual outcome: Clinically relevant non-major bleeding during intervention period at 20 ± 2 days; Group 1: 1/315, Group 2: 1/310 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 participant was not treated; Group 2 Number missing: 0 Protocol outcome 5: VTE at 7-90 days from hospital discharge - Actual outcome: Major VTE during intervention period at 20 ± 2 days; Group 1: 2/248, Group 2: 11/240; Comments: RRR 82.4 (95% CI 21.5 to96.1); p=0.01; "Major VTE" = Composite of symptomatic & asymptomatic proximal DVT, non-fatal PE and VTE-related deaths Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68, Reason: 1 participant was not treated + Venography not performed for 44 participants + Venography was of poor quality in 18 participants + 5 had unilateral venography; Group 2 Number missing: 70, Reason: Venography not performed for 42 participants + Venography was of poor quality in 17 participants + 11 had unilateral venography - Actual outcome: Major VTE during intervention and follow-up period at Up to 90 days; Group 1: 3/248, Group 2: 11/240; Comments: RRR 73.6 (95% CI 6.6 to 92.5); p=0.03 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68, Reason: 1 participant was not treated + Venography not performed for 44 participants + Venography was of poor quality in 18 participants + 5 had unilateral venography; Group 2 Number missing: 70, Reason: Venography not performed for 42 participants + Venography was of poor quality in 17 participants + 11 had unilateral venography	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Caprini 1983[42]
Study type	Systematic Review
Number of studies (number of participants)	1 (n=102)
Countries and setting	Conducted in USA; Setting: Department of surgery
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 72 hours + follow up not reported
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Patients taking anti-coagulants, sensitive to iodine or having operations on the breast or leg
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: 92.3% >40 years. Gender (M:F): 31:46. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (16.7% malignant condition). 2. Acute/elective: Not applicable 3. BMI : Not applicable(26% 'obese'). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Intermittent pneumatic compression devices - Full leg. Long TED stockings applied bilaterally upon all patients during the preoperative period. Patients were then randomised to either SCD or TED. Prior to onset of anesthesia, the TES were removed and IPCD applied to those in SCD group. This was maintained for at least 72 hours or until the patient was ambulatory. When the IPCD was removed, stockings were reapplied until discharge. Duration at least 3 days. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=39) Intervention 2: Anti-embolism stockings - Above knee. Long TED stockings applied bilaterally upon all patients during the preoperative period. Patients were then randomised to either SCD or TED. Those in the TED group wore stockings until discharge. Duration until discharge. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Supported in part by a grant from the Kendall Corporation and the Dee and Moody Fund, Evanston Hospital, Evanston, Illinois)

Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Chandhoke 1992[48]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 1-2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major open urological operation
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Major open urological operation lasting more than 2 hours
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): IPCD group: 67.5 (7.1), warfarin group: 66.1 (6.4). Gender (M:F): 99:1. Ethnicity: 1
Further population details	1. Active cancer: Active cancer (99% urological malignancy). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Open surgery 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Intermittent pneumatic compression devices - Full leg. Sequential leg and thigh intermittent pneumatic leg compression was instituted intraoperatively and continued for 5 days or until the patient became fully ambulatory . Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=53) Intervention 2: Vitamin K antagonists - Warfarin (variable dose). Low dose warfarin prophylaxis was begun on the night of the operation and continued postoperatively until the patient was discharged from hospital (1 to 2 weeks). The goal of low dose warfarin prophylaxis was to achieve a prothrombin time of approximately 1.5 times the preoperative value by 3 or 4 days postoperatively. The dose of warfarin was adjusted thereafter to maintain the prothrombin time at this level (approximately 16-18 seconds). Duration 1-2 weeks. Concurrent medication/care: Not repored. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FULL LEG versus WARFARIN (VARIABLE DOSE)	

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 1-2 weeks; Group 1: 0/47, Group 2: 0/53 Risk of bias: All domain - --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 1-2 weeks; Group 1: 2/47, Group 2: 0/53 Risk of bias: All domain - --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 1-2 weeks; Group 1: 1/47, Group 2: 0/53 Risk of bias: All domain - --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Clarke-pearson 1983[52]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in USA; Setting: Division of Gynecologic Oncology, Duke University Medical Center
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 42 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients undergoing a major operative procedure for known or presumed gynecologic malignancy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing a major operative procedure for known or presumed gynecologic malignancy
Exclusion criteria	Patients with evidence of thrombosis on preoperative fibrinogen 1 counting and/ore impendence plethysmography, patients having received anticoagulants within 6 weeks preoperatively, and patients with decreased platelet counts (less than 100,000/mm³) or a preoperative partial thromboplastin time or prothrombin time greater than one and one half times the control value
Recruitment/selection of patients	All admitted patients
Age, gender and ethnicity	Age - Other: 20-70+. Gender (M:F): Female. Ethnicity: White = 76.2%, black = 23.8%
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=95) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000 U of sodium heparin (The Upjohn Company, Kalamazoo, Michigan) subcutaneously 2 hours preoperatively and every 12 hours postoperatively for the first 7 postoperative days. Duration 7 days. Concurrent medication/care: Foot of the bed was elevated 20-30 degrees above the horizontal, and early postoperative ambulation. Indirectness: No indirectness (n=105) Intervention 2: No treatment - Usual care. No specific thromboembolic prophylaxis. Duration 7 days. Concurrent medication/care: Foot of the bed was elevated 20-30 degrees above the horizontal, and early postoperative ambulation. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 42 days; Group 1: 11/88, Group 2: 11/97 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: ; Group 2 Number missing: 8 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 42 days; Group 1: 4/88, Group 2: 0/97 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: ; Group 2 Number missing: 8 Protocol outcome 3: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 42 days; Group 1: 0/88, Group 2: 1/97 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: ; Group 2 Number missing: 8	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Clarke-pearson 1984[53]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=209)
Countries and setting	Conducted in USA; Setting: Division of Gynecologic Oncology, Duke University Medical Centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 42 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major surgery for known or presumed gynecologic malignancies
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients having major surgery for known or presumed gynecologic malignancies
Exclusion criteria	Patients with acute venous thromboembolic complications within 3 months of surgery and those who had received anticoagulants within 6 weeks of the operative procedure
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): Female. Ethnicity: Not reportes
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=105) Intervention 1: Intermittent pneumatic compression devices - Below knee. External pneumatic calf compression, applied at the time of induction of anesthesia in the operating room, and continued until discharge from recovery from or through the first 24 hours postoperatively. Duration 24 hours. Concurrent medication/care: Foot of beds were elevated 20-30 degrees and were encouraged to ambulate in the immediate post operative period. Antiembolism stockings were not worn. Indirectness: No indirectness (n=104) Intervention 2: No treatment - Usual care. No specific thromboembolic prophylaxis. Duration Not reported. Concurrent medication/care: Foot of beds were elevated 20-30 degrees and were encouraged to ambulate in the immediate post operative period. Antiembolism stockings were not worn. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus USUAL CARE	

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 42 days; Group 1: 14/97, Group 2: 11/97 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 8 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 42 days; Group 1: 4/97, Group 2: 1/97 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 8 Protocol outcome 3: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 42 days; Group 1: 1/97, Group 2: 1/97 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 8	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Clarke-pearson 1984[55]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=107)
Countries and setting	Conducted in USA; Setting: Division of Gynecologic Oncology, Duke Medical Center
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 42 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major surgery for known or presumed gynaecologic malignancies
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Major surgery for known or presumed gynaecologic malignancies
Exclusion criteria	Patients who had received anticoagulants within 6 weeks of surgery, or patients with acute venous thromboembolic complications
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: 20-70+. Gender (M:F): Female. Ethnicity: White 68.2%, black 28%, other 3.7%
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: Intermittent pneumatic compression devices - Below knee. External pneumatic calf compression device (Venogyne, Lyne-Nicholson, Inc., Needham Heights, MA), applied at the time of induction of anesthesia in the operation room. Calf compression was maintained intraoperatively and throughout the first 5 postoperative days. The sleeves were removed only when the patient was out of bed to ambulate. Duration 5 days. Concurrent medication/care: Both groups had the foot of their beds elevated to 20-30 degrees and were encouraged to ambulate in the immediate postoperative period. Indirectness: No indirectness (n=57) Intervention 2: No treatment - Usual care. No specific prophylaxis. Duration Not reported. Concurrent medication/care: Both groups had the foot of their beds elevated to 20-30 degrees and were encouraged to ambulate in the immediate postoperative period. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus USUAL CARE Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 42 days; Group 1: 0/55, Group 2: 0/52 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: ; Group 2 Number missing: 5 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 42 days; Group 1: 5/55, Group 2: 17/52 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: ; Group 2 Number missing: 5 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 42 days; Group 1: 2/55, Group 2: 1/52 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: ; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Clarke-pearson 1993[54]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=218)
Countries and setting	Conducted in USA; Setting: Division of Gynecologic Oncology
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major surgery for presumed or known gynaecologic malignancy
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Patients were stratified before randomisation if they were to undergo a pelvic exeneration
Inclusion criteria	Patients having major surgery for presumed or known gynaecologic malignancy
Exclusion criteria	Patients with a past history of a bleeding diathesis, thromboembolism within the past 3 months, anticoagulant use in the previous 6 weeks
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): UFH group: 57 (22-89), IPCD group: 55 (27-84). Gender (M:F): Female. Ethnicity: White 78.8%, other 21.2%
Further population details	1. Active cancer: Not applicable (Mixed 76.4%). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=107) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Low dose heparin, 5000U given subcutaneously at 2pm, 10pm and 6am before starting surgery at 8am. If a patient was admitted several days before surgery, heparin was started on admission and continued every 8 hours until surgery. Postoperatively, patients received 5000U of heparin every 8 hours for 7 days. If the patient was not fully ambulatory byt the 7th day, heparin was continued until full ambulation was established. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=101) Intervention 2: Intermittent pneumatic compression devices - Below knee. Intermittent pneumatic calf compression (Venodyne, Needham, Mass) initiated at the induction of anesthesia and continued while the patient was in the operating room, recovery room, and recumbent in their hospital bed. IPCD was continued for 5 days, or until the patient ambulated fully. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus BELOW KNEE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 30 days; Group 1: 7/107, Group 2: 4/101 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 10 patients excluded but not reported which groups they were in ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 30 days; Group 1: 0/107, Group 2: 0/101 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 10 patients excluded but not reported which groups they were in ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Coe 1978[60]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=83)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients undergoing open urological operations
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing open urological operations
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Intervention 1 = 63 (16) intervention 2 = 55 (11), control = 51 (18) . Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Open surgery 5. Renal impairment: Not applicable
Indirectness of population	--
Interventions	(n=28) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Sodium heparin (5000U subcutaneously) 2 hours before the operation and every 12 hours thereafter for the duration of their hospital stay. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=31) Intervention 2: Intermittent pneumatic compression devices - Below knee. External pneumatic compression of both calves by means of inflatable boots. Applied after induction of anesthesia and was maintained during the operative procedure and for the duration of hospitalisation. Short periods were allowed in which the boots were removed for patient comfort, nursing care, and ambulation. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=24) Intervention 3: No treatment - Usual care. Control group. No further details. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus BELOW KNEE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at Not reported; Group 1: 6/28, Group 2: 2/29
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not all important factors reported e.g. gender; Group 1 Number missing: 0; Group 2 Number missing: 2

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Not reported; Group 1: 1/28, Group 2: 1/29
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not all important factors reported e.g. gender; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at Not reported; Group 1: 6/28, Group 2: 6/24
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not all important factors reported e.g. gender; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Not reported; Group 1: 1/28, Group 2: 1/24
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not all important factors reported e.g. gender; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at Not reported; Group 1: 2/29, Group 2: 6/24

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not all important factors reported e.g. gender; Group 1 Number missing: 2; Group 2 Number missing: 0 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 1/29, Group 2: 1/24 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not all important factors reported e.g. gender; Group 1 Number missing: 2; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	EMRO trial: Gonzalez 1996[124]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=166)
Countries and setting	Conducted in Spain; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Elective abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients of both sexes, over 40 years of age, undergoing elective abdominal surgery who had previously signed the informed consent
Exclusion criteria	Pregnancy, cerebral or gastrointestinal bleeding, allergy to heparin and/or iodine contrast medium, DVT and/or PE in the 6 previous months, bleeding disease and thrombophilia, heparin induced thrombocytopenia or platelet count <100,000/mm³, arterial hypertension, severe renal failure requiring hemodialysis, chronic hepatic failure, oral anticoagulant treatment or treatment with unfractionated heparin or LMWH in previous 24 hours, antiplatelet drugs in previous 7 days, participation in another trial
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 61.48 (12.21), UFH: 63.01 (11.39). Gender (M:F): 65:101. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Excluded severe renal failure requiring hemodialysis).
Indirectness of population	No indirectness

Interventions	(n=84) Intervention 1: Low molecular weight heparin (not licensed in UK) - Bemiparin (2500 units once daily - 3500 units once daily). RO-11 2500U administered 2 hours before surgery and a placebo injection 12 hours after the first one. Thereafter, and during the following 7 days, RO-11 was administered once daily in the morning, and the placebo 12 hours after the morning injection. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=82) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Calcium heparin 5000U administered 2 hours before he surgery and 12 hours after the first dose. Thereafter, 5000U were administered every 12 hours for 7 days. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEMIPARIN (2500 UNITS ONCE DAILY - 3500 UNITS ONCE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 8 days; Group 1: 0/84, Group 2: 0/82
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 8 days; Group 1: 0/84, Group 2: 0/82
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 8 days;
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening

clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 8 days; Group 1: 0/84, Group 2: 5/82 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	ENOXACAN II trial: Bergqvist 2002[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=501)
Countries and setting	Conducted in Multiple countries
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	--
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Age, gender and ethnicity	Age - --: . Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Elective 3. BMI : Mixed (Range 15-45). 4. Laparoscopic/open surgery: Open surgery 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Excluded renal insufficiency).
Indirectness of population	No indirectness
Interventions	(n=253) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 40mg enoxaparin (Lovenox or Clexane, Aventis Pharmaceuticals, Paris), once daily. First dose given 10-14 hours preoperatively, for 6-10 days. Then randomised to 40mg enoxaparin for a further 19-21 days for a total of 25-31 days. Duration 25-31 days. Concurrent medication/care: AES were allowed but IPCD and electrical calf stimulation was not. Indirectness: No indirectness (n=248) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 40mg enoxaparin (Lovenox or Clexane, Aventis Pharmaceuticals, Paris), once daily. First dose given 10-14 hours preoperatively, for 6-10 days. Then randomised to placebo for a further 19-21 days for a total of 25-31 days. Duration 6-10 days. Concurrent medication/care: AES were allowed but IPCD and electrical calf stimulation was not. Indirectness: No indirectness
Funding	Academic or government funding (Supported by a grant from the Swedish Medical Research Council and by Aventis Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN EXTENDED DURATION (20MG ONCE DAILY – 60MG TWICE DAILY) versus ENOXAPARIN STANDARD DURATION (20MG ONCE DAILY – 60MG TWICE DAILY) Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 2 months; Group 1: 3/165, Group 2: 6/167 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 88; Group 2 Number missing: 81 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 3 months; Group 1: 9/165, Group 2: 21/167 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 88; Group 2 Number missing: 81 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 3 months; Group 1: 0/165, Group 2: 2/167 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 88; Group 2 Number missing: 81 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 3 months; Group 1: 3/253, Group 2: 1/248 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 3 months; Group 1: 0/165, Group 2: 1/167 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 88; Group 2 Number missing: 81	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration

of study; Technical complications of mechanical interventions at duration of study;

Study	Fasting 1985[100]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=97)
Countries and setting	Conducted in Denmark; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Elective major surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged above 40 years old, admitted to the County Hospital of Aarhus for elective general surgery, involving general anesthesia of more than one hours duration
Exclusion criteria	Patients already treated with anticoagulants, patients with severe heart failure or hemorrhagic diathesis were not included in the study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): UFH group: 60 (39-80), AES group: 60 (39-87). Gender (M:F): 49:48. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (31.9% malignant cases). 2. Acute/elective: Elective 3. BMI : Not applicable(20.6% obese (>1.25 Natvig's Index)). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: Anti-embolism stockings - Above knee. AES of thigh length, starting the evening before operation and continued for 5 days after the operation and were only stopped when patients were mobile . Duration At lest 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=51) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Low dose heparin 5000U was given subcutaneously, starting the 2-3 hours before operation and continued every 12 hours for at least 5 days and only stopped when patients were mobile. Duration At least 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABOVE KNEE versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)	

Protocol outcome 1: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Not reported; Group 1: 0/52, Group 2: 0/45 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 6 Protocol outcome 2: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at Not reported; Group 1: 0/52, Group 2: 1/45 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 6	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Fricker 1988[108]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in France; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Up to 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Surgery of a primary of secondary malignant tumour of the abdomen or pelvis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were 40 years of age or older and awaiting surgery of a primary or secondary malignant tumour of the abdomen or pelvis, lasting at least 30 minutes and under general anesthesia
Exclusion criteria	Infectious endocarditis, previous bleeding disorders, hepato-cellular failure with a prothrombin time less than 50%, serum creatinine levels high than 200 µmol 1-1, cerebral haemorrhage in the last 6 months, suspected hypersensibility to heparin or iodine, anticoagulation stopped for less than 14 days before operation, treatment by Amiodaron stopped for less than 3 months before surgery
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): LMWH group: 58.2 (40-78), UFH group: 57.0 (41-75). Gender (M:F): 8:72. Ethnicity: Not reported
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 2500U Fragmin 2 hours before surgery and 12 hours after first injection every morning for 10 days. Duration 10 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=40) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Calcium heparin 5000U injection 2 hours before surgery and then at 8 hour intervals for the next 10 days. Duration 10 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 8 weeks; Group 1: 3/40, Group 2: 1/40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 8 weeks; Group 1: 0/40, Group 2: 5/40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 8 weeks; Group 1: 2/40, Group 2: 1/40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Gallus 1973[116]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=226)
Countries and setting	Conducted in Canada; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People having elective surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over 40 years old admitted for elective surgery
Exclusion criteria	Bleeding tendency, iodine allergy, or history of pulmonary embolism or venous thrombsis within the past year
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): UFH group: 60 (44-79), control group: 59 (41-83). Gender (M:F): 92:134. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Cancer 15.5%). 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=108) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH 5000U of aqueous sodium heparin by subcutaneous injection 2 hours before surgery and then 3 times daily starting 8 to 10 hours after the preoperative dose. Treatment was continued until the patient was fully mobile. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=118) Intervention 2: No treatment - Usual care. Untreated group. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Supported in part by an Ontario Provincial Health Research grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge

- Actual outcome: DVT at Up to 32 days; Group 1: 1/108, Group 2: 4/118 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Gallus 1976[115]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=820)
Countries and setting	Conducted in Canada; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People having abdominothoracic surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients more than 40 years old who had had major elective abdominothoracic surgery
Exclusion criteria	Contraindication to heparin treatment, thromboembolism had occurred within previous 12 months
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (range): UFH group: 59 (40-87), control group: 60 (40-87). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 17%). 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=408) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 50000U aqueous heparin sodium by subcutaneous injection two hours before surgery and then eight hourly, starting 8-10 hours after surgery. Treatment continued for 7 days or until discharged/ambulant. Duration 7 days (mean 6.4, range 1-20 days). Concurrent medication/care: Not reported. Indirectness: No indirectness (n=412) Intervention 2: No treatment - Usual care. Untreated group. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Supported by Ontario Provincial Government Health research grants and the St Josephs Hospital Foudation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 4/408, Group 2: 12/412 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Gao 2012[117]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=116)
Countries and setting	Conducted in China; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT was diagnosed using colour Doppler flow imaging. PE was diagnosed using computed tomographic pulmonary angiography.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with high risk factors for DVT (e.g. history of VTE, hypercoagulopathy, aged > 60 years, heart disease, varicose veins) who underwent gynaecological pelvic surgery for various gynaecological diseases
Exclusion criteria	Thrombophlebitis; acute deep venous thrombosis; platelet count < (100x10^9)/L or coagulopathy; spontaneous bleeding in the last 6 months; congestive heart failure / pulmonary oedema / leg oedema; haematologic disorders; leg abnormalities / severe atherosclerosis of lower extremity vessels / ischaemic vascular diseases / severe leg deformities
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): AES+IPC 60.9 (11.6) vs. AES only 59.4 (10.2). Gender (M:F): 0:108. Ethnicity: Implicitly assumed to be Chinese
Further population details	1. Active cancer: Active cancer (No. in (AES+IPC vs. AES only): Malignant tumour (16 vs. 19), Ovarian cancer (8 vs. 7), Endometrial carcinoma (3 vs. 6), Cervical cancer (5 vs. 6)). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Systematic review: mixed (No. in (AES+IPC vs. AES only): Laparotomy (10 vs. 17), Laparoscopic surgery (32 vs. 28), Vaginal surgery (10 vs. 11)). 5. Renal impairment: Not applicable
Extra comments	It is unclear at which exact point the participants were randomised to the interventions. It is reported that 116 patients were enrolled during the study period and 8 were excluded (but reasons for exclusion are not given), then subsequently 2 had their surgeries cancelled, 4 did not receive ultrasonography and 2 complained of sleep disturbances and discomfort due to IPC, and that ultimately 108 patients completed the study. However, it is reported several times in the article that 52 patients and 56 patients were randomly assigned to the AES+IPC and AES group, respectively. This gives the impression that 108 patients were randomised but this may not be the original number of people randomised.
Indirectness of population	Serious indirectness: Incidence of VTE is lower in Asian populations. Ethnicity of the participants is not reported in this

	study, however, it has been implicitly assumed that majority are Chinese.
Interventions	(n=52) Intervention 1: Intermittent pneumatic compression devices - Full leg. Three-chamber SCD, Kendall®, USA (Tyco International Inc.), applied during and after operation, sequentially for 11 seconds with pressures of 45, 35 and 30mmHg at the ankle, calf and thigh, respectively. Duration Until ambulation (exact duration unclear). Concurrent medication/care: AES applied pre-operatively only. Indirectness: No indirectness (n=56) Intervention 2: Anti-embolism stockings - Mixed above/below knee. Adequately sized AES for above knee and below knee, worn pre-operatively. Duration Until normal ambulation (exact duration unclear). Concurrent medication/care: None. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IPC+AES versus AES ONLY

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: Number of DVT at Unclear; Group 1: 5/52, Group 2: 14/56
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Data of 8 participants who were excluded (for various reasons) are missing and it is unclear whether they were excluded before or after randomisation. Moreover, the exact timings of interventions and the time points at which the data were collected are not reported.; Indirectness of outcome: No indirectness, Comments: The time period for outcome measurement has not been specified.; Group 1 Number missing: , Reason: The study reports that 116 patients were enrolled during the study period but eight were excluded, and subsequently, 2 had their surgeries cancelled, 4 did not receive ultrasonography and 2 complained of sleep disturbances and discomfort due to IPC. The study states that as a result, 108 patients completed the study.; Group 2 Number missing: , Reason: Unclear exactly how many are missing from each group.

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Unclear; Group 1: 1/52, Group 2: 1/56
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Data of 8 participants who were excluded (for various reasons) are missing and it is unclear whether they were excluded before or after randomisation. Moreover, the exact timings of interventions and the time points at which the data were collected are not reported.; Indirectness of outcome: No indirectness, Comments: The time period for outcome measurement has not been specified.; Group 1 Number missing: , Reason: The study reports that 116 patients were enrolled during the study period but eight were excluded, and subsequently, 2 had their surgeries cancelled, 4 did not receive ultrasonography and 2 complained of sleep disturbances and discomfort due to IPC. The study states that as a result, 108 patients completed the study.; Group 2 Number missing: , Reason: Unclear exactly how many are missing from each group.

Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Gordon-smith 1972[125]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=98)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal operation or one of the following operations: prostatectomy, nephrectomy, ureterolithotomy, and radical mastectomy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 40 years of age undergoing either a major abdominal operation or one of the following operations: prostatectomy, nephrectomy, ureterolithotomy, and radical mastectomy.
Exclusion criteria	Patients with a history of hepatitis, patients having elective splenectomy, patients who were the subject of a separate study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): UFH group: 61.5 (10.2), control group: 63.6 (12.1). Gender (M:F): 49:49. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (32.7% malignant). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U sodium heparin given subcutaneously 1 hour before operation, and thereafter the same dose was given 12 hourly until the fifth post operative day. Duration 5 days. Concurrent medication/care: No other method of prophylaxis was used apart form routine ward exercises, physiotherapy and mobilisation according to the wishes of the surgeon in charge of each patient. Indirectness: No indirectness (n=50) Intervention 2: No treatment - Usual care. No heparin. Duration Not reported . Concurrent medication/care: No other method of prophylaxis was used apart form routine ward exercises, physiotherapy and mobilisation according to the wishes of the surgeon in charge of each patient. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 4/48, Group 2: 21/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 2/48, Group 2: 0/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Hartl 1990[139]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=250)
Countries and setting	Conducted in Austria; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Elective abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over the age of 40 who had to undergo elective abdominal surgery except appendectomy and herniotomy were included
Exclusion criteria	Volume substitution with dextran or HES, oral anticoagulant therapy, patients on heparin, administration of drugs containing platelet function inhibitors, coagulation defects and recent preoperative thrombosis ad well as allergy to iodine or heparin
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 64.6 (11.3), UFH group: 62.9 (12.6). Gender (M:F): 144:106. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Cancer 29.6%). 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=126) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Fragmin 2500U once daily, started 2 hours preoperatively and was maintained until the patients were fully mobilized but at least for one week. Duration 7 days. Concurrent medication/care: Not reported (n=124) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH 5000IU twice daily, started 2 hours preoperatively and was maintained until the patients were fully mobilized but at least for one week. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at Not reported; Group 1: 5/126, Group 2: 3/124 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 5/112, Group 2: 5/115 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14; Group 2 Number missing: 9 Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Not reported; Group 1: 2/112, Group 2: 15/115 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14; Group 2 Number missing: 9 Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at Not reported; Group 1: 1/112, Group 2: 1/115 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14; Group 2 Number missing: 9	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Hata 2016[140]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=298)
Countries and setting	Conducted in Japan; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: 5 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with urological malignancy aged 40 or older, scheduled for surgery at Jikei University Hospital from January 2011-December 2012, considered candidates for open or laparoscopic surgery of >45 minutes in length and with a life expectancy of at least 6 months after surgery
Exclusion criteria	Body weight >40kg; hypersensitivity to fondaparinux or LMWH; contraindication to anticoagulant therapy; active bleeding; documented bleeding disorder or thrombocytopenia; perioperative VTE within the previous year; sever hepatic dsyfunction; severe renal dysfunction (eGFR <30mL/min/1.73m²); concurrent disorder such as gastrointestinal ulceration or diverticulitis, colitis, bacterial endocarditis, severe diabetes mellitus, severe hypertension or disseminated intravascular coagulation; hemorrhagic stroke; brain, spine or eye surgery within the previous 3 months; HIT; or pregnancy
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Fonda group 64.7 (7.5); LMWH group 63.9 (7.5). Gender (M:F): 282:16. Ethnicity: Not reported
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable (Mixed). 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2)
Indirectness of population	No indirectness
Interventions	(n=152) Intervention 1: Fondaparinux - Fondaparinux (all doses). Fondaparinux (2.5mg), once daily, starting on postoperative day 2 until day 5. Plus UFH (5000U) started 6 hours after wound closure and continued every 12 hours until the day after surgery. Plus mechanical thromboprophylaxis (AES and IPCD) worn until ambulatory. If eGFR ranged from 30-50 mL/min/1.732 and the risk of bleeding was high, prophylaxis could be reduced to 1.5mg (fondaparinux) or 2000U daily (enoxaparin), at the discretion of the physician. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=146) Intervention 2: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice

	daily). LMWH (enoxaparin, 2000U, twice daily) starting on postoperative day 2 until day 5. Plus UFH (5000U) started 6 hours after wound closure and continued every 12 hours until the day after surgery. Plus mechanical thromboprophylaxis (AES and IPCD) worn until ambulatory. If eGFR ranged from 30-50 mL/min/1.732 and the risk of bleeding was high, prophylaxis could be reduced to 1.5mg (fondaparinux) or 2000U daily (enoxaparin), at the discretion of the physician. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (This study was financially supported by Glaxo Smith Kline K. K. and Kalen Pharmaceutical Co. LTD.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX (ALL DOSES) versus ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) Protocol outcome 1: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 0/130, Group 2: 2/128 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22, Reason: ; Group 2 Number missing: 18 Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Not reported; Group 1: 2/152, Group 2: 1/146 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Hauch 1988[141]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Denmark; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Elective major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 40 or over scheduled for elective major abdominal surgery, provided it was possible to place a central venous catheter and the expected postoperative hospitalisation was at least 7 days
Exclusion criteria	Hepatic of renal insufficiency, normosion test below 60%, haemorrhagic diathesis, history of cerebral vascular disease, pregnancy, thrombocytopenia, anticoagulation or fibrinolytic treatment within one month before surgery, untreated hypertension and allergy to heparin or iodine.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): low dose group: 68 (41-85), standard dose group: 72 (40-88). Gender (M:F): 13:22. Ethnicity: Not stated
Further population details	1. Active cancer: 2. Acute/elective: 3. BMI : 4. Laparoscopic/open surgery: 5. Renal impairment:
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Low molecular weight heparin (licensed in UK) - Tinzaparin (2,500 units once daily – 9,000 units once daily). LMWH 2500U administered subcutaneously 2 hours preoperatively and once daily in the postoperative period for 7 days or until discharge. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=20) Intervention 2: Low molecular weight heparin (licensed in UK) - Tinzaparin (2,500 units once daily – 9,000 units once daily). LMWH 3500U administered subcutaneously 2 hours preoperatively and once daily in the postoperative period for 7 days or until discharge. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TINZAPARIN LOW DOSE (2,500 UNITS ONCE DAILY – 9,000 UNITS ONCE DAILY) versus TINZAPARIN STANDARD DOSE (2,500 UNITS ONCE DAILY – 9,000 UNITS ONCE DAILY) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 7 days; Group 1: 2/16, Group 2: 0/19 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Low dose group had a lot more predisposing risk factors; Group 1 Number missing: 6; Group 2 Number missing: 1 Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 7 days; Group 1: 0/16, Group 2: 0/19 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Low dose group had a lot more predisposing risk factors; Group 1 Number missing: 6; Group 2 Number missing: 1 Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 7 days; Group 1: 0/16, Group 2: 1/19 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Low dose group had a lot more predisposing risk factors; Group 1 Number missing: 6; Group 2 Number missing: 1 Protocol outcome 4: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 7 days; Group 1: 0/16, Group 2: 0/19 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Low dose group had a lot more predisposing risk factors; Group 1 Number missing: 6; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical

interventions at duration of study;

Study	Holford 1976[149]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=98)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Elective major surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over 40 years of age about to undergo elective major surgery
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Stockings group: 58 (10.7), control 59 (9.5). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 20% malignancy). 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Anti-embolism stockings - Above knee. AES, full length, fitted 12 hours before operation and not removed until the patient was fully ambulant, usually on the 4th or 5th day after the operation. Duration 4-5 days. Concurrent medication/care: No other specific method for preventing DVT was used, but all patients underwent the usual ward routine of encouraging early leg activity while in bed and early ambulation whenever possible. Indirectness: No indirectness (n=47) Intervention 2: No treatment - Usual care. Control group. Duration Not reported. Concurrent medication/care: No other specific method for preventing DVT was used, but all patients underwent the usual ward routine of encouraging early leg activity while in bed and early ambulation whenever possible. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Stockings provided by the Kendall Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABOVE KNEE versus USUAL CARE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge

- Actual outcome: All-cause mortality at Not reported; Group 1: 0/48, Group 2: 0/47 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 11/48, Group 2: 23/47 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 0/48, Group 2: 1/47 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Kaaja 1992[161]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in Finland; Setting: Two centres
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3-4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Abdominal hysterectomy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were enrolled in the trial if they were aged between 35 and 75, were scheduled for abdominal hysterectomy and under general anaesthesia and exhibited at least one of the following risk factors: a history of DVT and/or PE, varicose veins, congestive heart failure, chronic bronchitis, estrogen treatment, obesity (>20% ideal body weight) and carcinoma of the uterine corpus
Exclusion criteria	Known bleeding tenedency, abnormal coagulation test results, thrombocytopenia, acute bleeding, severe arterial hypertenteion, impaired renal or hepatic function, hypersensitivity to heparin, metabisulphite or dihydroergotamine or mental disorder
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 48.1 (8.6), UFH group: 50.4 (8.8). Gender (M:F): Female. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (25% malicnancy). 2. Acute/elective: Not applicable 3. BMI : Mixed (33.8% obese). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Excluded impaired renal function).
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). 20mg enoxaparin subcutaneously once a day, administered 2 hours before operation and continued for 3 day. Duration 3 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=31) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Heparin 5000U twice daily, administered 2 hours before operation and continued for 3 days. Duration 3 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 3-4 weeks; Group 1: 0/37, Group 2: 0/31
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 35.1% versus 51.6% obese; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 3-4 weeks; Group 1: 0/37, Group 2: 0/31
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 35.1% versus 51.6% obese; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 3-4 weeks; Group 1: 0/37, Group 2: 6/31
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 35.1% versus 51.6% obese; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Kakkar 1972[166]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged over 40 years undergoing major surgery
Exclusion criteria	Patients with clinical signs of recent DVT, operations on the thyroid gland, patents already on prophylactic anticoagulants
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): UFH group: 63.7 (42-90), control group: 64.4 (40-88). Gender (M:F): 45:33. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (34.6% malignancy). 2. Acute/elective: Not applicable 3. BMI : Mixed (24.4% obese (undefined)). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Calcium heparin injected 2 hours before operation and thereafter every 12 hours for 7 days. Duration 7 days. Concurrent medication/care: Routine physiotherapy was used in all patients. Indirectness: No indirectness (n=39) Intervention 2: No treatment - Placebo. Placebo solution of gelatin, injected 2 hours before operation and thereafter every 12 hours for 7 days. Duration 7 days. Concurrent medication/care: Routine physiotherapy was used in all patients. Indirectness: No indirectness
Funding	Other (Financial support from the Kings College Hospital Research Trust, Pfizer Ltd financed a research fellowship)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler)

ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 10 days; Group 1: 3/39, Group 2: 17/39 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 0/39, Group 2: 0/39 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Kakkar 1993[165]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3938)
Countries and setting	Conducted in United Kingdom; Setting: 19 hospitals in the Midlands and South East England
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 4-8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major elective abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female patients over 40 years of age, scheduled to undergo major elective abdominal surgery
Exclusion criteria	Known allergy to heparin, taking oral anticoagulants immediately before admission, had had a severe haemorrhagic episode in the previous 3 months unrelated to the proposed surgery, had a known bleeding diahesis, scheduled for reoperation during the study period, were women of childbearing age not actively avoiding pregnancy, or had any other contraindication to heparin
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: 40-80+. Gender (M:F): 1314:2495. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 36.9%). 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=1960) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 2500U once daily plus placebo injection, starting 1-4 hours before surgery for at least 5 postoperative days and discontinued when the patient was fully mobile. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=1978) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U UFH, begun 1-4 hours before surgery and continued for at least 5 days postoperatively and only discontinued when the patient was fully mobile . Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Other (Supported by a grant from Thrombosis Research Trust and medication provided by Kabi Pharmacia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 4-8 weeks; Group 1: 63/1894, Group 2: 47/1915 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 66; Group 2 Number missing: 62 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 4-8 weeks; Group 1: 11/1894, Group 2: 11/1915 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 66; Group 2 Number missing: 62 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 4-8 weeks; Group 1: 8/1894, Group 2: 11/1915 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 66; Group 2 Number missing: 62 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 4-8 weeks; Group 1: 69/1894, Group 2: 91/1915 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 66; Group 2 Number missing: 62 Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 4-8 weeks; Group 1: 5/1894, Group 2: 3/1915 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 66; Group 2 Number missing: 62	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration

of study; Technical complications of mechanical interventions at duration of study;

Study	Koller 1986-1[176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=43)
Countries and setting	Conducted in Switzerland; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Elective visceral surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients between 20 and 80 years undergoing the following elective operations: thoracotomy, cholecystectomy, colon resection, proximal selective vagotomy, herniotomy, breast operation and other visceral operations
Exclusion criteria	Previous history of a bleeding disorder, pregnancy, ingestion of acetylsalicylic during the last 5 days before operation and any type of anticoagulation before the operation
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 52.8 (15.0), UFH group: 57.3 (15.1). Gender (M:F): 28:15. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 7500U once daily, first dose given 1 hour before operation, the second at 6pm, thereafter 12 hourly for a minimum of 5 days. The evening injection contained placebo. Duration 5 days. Concurrent medication/care: Not reported (n=20) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000 U twice daily. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Study supported by KabiVitrum AB, Stockholm, Sweden)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 30 days; Group 1: 0/23, Group 2: 0/20 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 30 days; Group 1: 0/23, Group 2: 0/20 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 30 days; Group 1: 6/23, Group 2: 1/20 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Koller 1986-2[176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=146)
Countries and setting	Conducted in Switzerland
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	--
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Age, gender and ethnicity	Age - --: . Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 14.4% malgnancy). 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	--
Interventions	(n=75) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). 2500U once a day. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=75) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH 5000U twice daily. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 30 days; Group 1: 0/74, Group 2: 0/72
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3

	Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 30 days; Group 1: 2/74, Group 2: 1/72 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 30 days; Group 1: 0/74, Group 2: 1/72 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 30 days; Group 1: 17/74, Group 2: 23/72 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Kutnowski 1977[181]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in Belgium; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major urological operation
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 40 years or over admitted to the hospital for a major urological operation lasting more than half an hour and requiring at least 7 days of postoperative hospital care
Exclusion criteria	Patients with thyroid disease, recent venous thrombosis or lower limb amputation. Patients having emergency surgery, taking anticoagulants or antiaggregating drugs
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): UFH group: 70.5, control group: 60.7. Gender (M:F): 37:10. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 10.6% malignant disease). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U calcium heparin, given 2 hours before operation and then every 8 hours for 6 days. Duration 6 days. Concurrent medication/care: All patients underwent physiotherapy with passive and active exercises for the legs. Patients with varicose veins wore elastic stockings during and after operation. Indirectness: No indirectness (n=25) Intervention 2: No treatment - Placebo. 0.2ml distilled water. Duration 6 days. Concurrent medication/care: All patients underwent physiotherapy with passive and active exercises for the legs. Patients with varicose veins wore elastic stockings during and after operation. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO	

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reoprted; Group 1: 3/22, Group 2: 12/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference of 10 years in average age; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Lahnborg 1975[184]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=112)
Countries and setting	Conducted in Sweden; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 5 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major elective abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted for elective major abdominal surgery
Exclusion criteria	Patients with allergy to iodine or with cardiopulmonary disease
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): UFH group: 62 (40-86), control group: 63 (40-80). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH 5000U of sodium heparin, subcutaneously 2-5 hours before surgery and twice daily starting 12 hours after the preoperative dose and then for 5 days . Duration 5 days. Concurrent medication/care: All patients had physiotherapy before and after the operation, including leg and breathing exercises (n=54) Intervention 2: No treatment - Placebo. 0.5ml of 0.85% saline. Duration 5 days. Concurrent medication/care: All patients had physiotherapy before and after the operation, including leg and breathing exercises. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge

- Actual outcome: All-cause mortality at 5 days; Group 1: 0/58, Group 2: 0/54 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 9/58, Group 2: 24/54 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Not reported; Group 1: 0/58, Group 2: 0/54 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Leizorovicz 1991[204]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1290)
Countries and setting	Conducted in France, United Kingdom; Setting: 23 centres located in France and the UK
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: General surgery (71.4% abdominal, 13.5% gynaecological, 9.8% urological, 5.3% thoracic)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing general surgery (abdominal, gynaecological, urological, thoracic, but not cardiac surgery) who were 40 years or older and in whom general anaesthesia longer than 30 minutes was anticipated. Only patients with at least one of the following risk factors were included: previous history of VTE, varicose veins, obesity, contraceptive pill, hormonal replacement therapy, chronic respiratory insufficiency, heart failure, malignancy, previous long bone fracture of lower limb, bed rest >5 days before surgery, predicted duration of surgery >4 hours, >60 years of age
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 61 (SD not reported). Gender (M:F): 513:777. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (38.5% malignancy). 2. Acute/elective: Elective 3. BMI : Not applicable (Obesity (overweight >20%) = 28%). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable

Indirectness of population	No indirectness
Interventions	(n=431) Intervention 1: Low molecular weight heparin (licensed in UK) - Tinzaparin (2,500 units once daily – 9,000 units once daily). Logiparin 2500U once a day, started 2 hours before surgical intervention. The second injection was given 12 hours later, and treatment was continued for at least 7 days and for a maximum of 10 days . Duration 7-10 days. Concurrent medication/care: Stockings and other forms of DVT prophylaxis were not allowed. Indirectness: No indirectness (n=430) Intervention 2: Low molecular weight heparin (licensed in UK) - Tinzaparin (2,500 units once daily – 9,000 units once daily). 3500U once a day starting 2 hours before surgical intervention. Duration 7-10 days. Concurrent medication/care: Stockings and other forms of DVT prophylaxis were not allowed. Indirectness: No indirectness (n=429) Intervention 3: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Sodium heparin 5000U twice daily. Duration 7-10 days. Concurrent medication/care: Stockings and other forms of DVT prophylaxis were not allowed. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TINZAPARIN LOW DOSE (2,500 UNITS ONCE DAILY – 9,000 UNITS ONCE DAILY) versus TINZAPARIN STANDARD DOSE (2,500 UNITS ONCE DAILY – 9,000 UNITS ONCE DAILY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 1 month; Group 1: 10/431, Group 2: 10/430
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 8 days; Group 1: 16/431, Group 2: 7/430
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy;

echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 1 month; Group 1: 4/431, Group 2: 1/430
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 1 month; Group 1: 14/431, Group 2: 10/430
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TINZAPARIN LOW DOSE (2,500 UNITS ONCE DAILY – 9,000 UNITS ONCE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 1 month; Group 1: 10/431, Group 2: 9/429
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 8 days; Group 1: 16/431, Group 2: 7/429
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: DVT at 8 days; Group 1: 16/431, Group 2: 7/429
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 1 month; Group 1: 4/431, Group 2: 2/429
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial,

intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 1 month; Group 1: 14/431, Group 2: 12/429 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TINZAPARIN STANDARD DOSE (2,500 UNITS ONCE DAILY – 9,000 UNITS ONCE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 1 month; Group 1: 10/430, Group 2: 9/429 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 1 month; Group 1: 1/430, Group 2: 2/429 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 1 month; Group 1: 10/430, Group 2: 12/429 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Marassi 1993[215]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Italy; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: elective major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged over 40 years and scheduled to undergo elective major abdominal surgery for cancer of the gastrointestinal tract
Exclusion criteria	Patients with severe renal or liver dysfunction, jaundice, abnormalities of haemostasis, active peptic ulcer, previous stroke
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): LMWH group: 64 (41-82), control group: 66 (47-79). Gender (M:F): 36:25. Ethnicity: Not reported
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable (Excluded severe renal dysfunction).
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Low molecular weight heparin (not licensed in UK) - Nadroparin (2850 units once daily - up to 57 units/kg once daily). Subcutaneous injection of Seleparina starting on the day of surgery, then daily for 7 days. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=33) Intervention 2: No treatment - Usual care. No form of prophylaxis . Duration 7 days . Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Supported in part by a grant from "Programma Nazionale di Ricerca Farmaci, Consorzio Antitrombotici")

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NADROPARIN (2850 UNITS ONCE DAILY - UP TO 57 UNITS/KG ONCE DAILY) versus USUAL CARE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge

- Actual outcome: All-cause mortality at 7 days; Group 1: 0/30, Group 2: 0/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 7 days; Group 1: 2/30, Group 2: 11/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Maxwell 2001[217]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=228)
Countries and setting	Conducted in USA; Setting: Gynecologic Onvology service at Duke University Medical Center
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal or pelvic surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients over 40 years of age admitted to the Gynecologic Oncology service at Duke University Medical Center, undergoing major abdominal or pelvic surgery for known or suspected gynecologic malignancy
Exclusion criteria	Deep vein thrombosis or pulmonary embolism in the previous 6 months, contraindication to heparin therapy, conduction anesthesia, history of heparin sensitivity, pregnancy, or history of coagulation abnormalities. Also, platelet count less than 100,000 or if the activated partial thromboplastin time or prothrombin time was over 1.5 times the control value
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): IPCD group: 62 (35-85), LMWH group: 60 (41-87). Gender (M:F): Female. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 75% cancer). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=106) Intervention 1: Intermittent pneumatic compression devices - Mixed full leg/below knee. External pneumatic compression sleeves, length not reported. Applied in the operating room with the induction of anesthesia and continued throughout the operative procedure as well as the first 5 days post operatively. When the patient was fully ambulatory, the device was temporarily removed and reinstituted when the patient returned to bed. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=105) Intervention 2: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin 2500U subcutaneously 1-2 hours before surgery. Post operatively patients received 2500U 12 hours after the first dose. After the perioperative split dose on the day of surgery, patients received a daily dose of 5000U, starting on the first postoperative days until the 5th postoperative day or day of discharge. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness

Funding	Study funded by industry (Supported in part by unrestricted educational grants from the Pharmacia Corporation and Venodyne, and the ACOG/Ethicon Research Award for Innovations in Gynecologic surgery)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED FULL LEG/BELOW KNEE versus DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 30 days; Group 1: 1/106, Group 2: 2/105 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 17 patients excluded but unclear which groups they were in; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 30 days; Group 1: 0/106, Group 2: 0/105 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 17 patients excluded but unclear which groups they were in; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Heparin-induced thrombocytopenia at duration of study - Actual outcome: Thrombocytopenia at 3 days; Group 1: 4/106, Group 2: 2/105 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 17 patients excluded but unclear which groups they were in; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only)

at up to 90 days from hospital discharge; Technical complications of mechanical interventions at duration of study;

Study	Mcleod 2001[222]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1349)
Countries and setting	Conducted in Canada; Setting: 10 university hospitals in Canada
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 9 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients undergoing colorectal surgery
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Before randomisation, patients were stratified by insitution, nature of disease and the extent of anticipated dissection
Inclusion criteria	All adult patients undergoing surgery during which part or all of their colon or rectum was resected or in whom a complete rectal dissection was performed were eligible, provided the procedure was performed under general anesthesia and was at least 1 hour long
Exclusion criteria	Patients were excluded if they required anticoagulant, antiinflammatory, or antiplatelet therapy that could not be discontinued, had hepatic or renal failure, had a history of a systemic bleeding diathesis or heparin induced thrombocytopenia, uncontrolled hypertension, hemorrhagic stroke or gastrointestinal hemorrhage in the previous 3 months, a major psychiatric disorder or a systemic allergy to contrast material, or were pregnant or lactating
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 52 (18), UFH group: 50 (17). Gender (M:F): 731:618). Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 35% cancer). 2. Acute/elective: Not applicable 3. BMI : Mixed (14.6% BMI >30%). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable (Excluded renal failure).
Indirectness of population	No indirectness
Interventions	(n=674) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 40mg subcutaneously once daily in the morning plus 2 placebo injections. Initiated 2 hours before surgery and one further placebo injection was given at 8pm on the day of surgery. Thereafter patients received injections for up to 10 days. Duration 10 days. Concurrent medication/care: Other methods of pharmacologic or mechanical prophylaxis including AES were not allowed, nor was the use of nonsteroidal antiinflammatory agents. Indirectness: No indirectness (n=675) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Calcium heparin 5000U subcutaneously every 8 hours. Initiated 2 hours before surgery and one further placebo injection was given at 8pm on the day of surgery. Thereafter patients received injections for up to 10 days. Duration 10 days. Concurrent medication/care: Other methods of pharmacologic or mechanical prophylaxis including AES were

	not allowed, nor was the use of nonsteroidal antiinflammatory agents. Indirectness: No indirectness
Funding	Study funded by industry (Supported by a grant from Rhone-Poulene Rorer Canada Inc)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 9 days; Group 1: 1/468, Group 2: 0/648 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 206; Group 2 Number missing: 207 Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 9 days; Group 1: 18/653, Group 2: 10/643 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 21; Group 2 Number missing: 32	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Nagata 2015[235]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=35)
Countries and setting	Conducted in Japan; Setting: Secondary/Tertiary care
Line of therapy	Not applicable
Duration of study	Intervention time: Up to 11 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: VTE was evaluated by chest, abdominal and lower extremities contrast-enhanced CT scan. VTE was diagnosed after discussion with board-certified radiologists who were blinded to interventions.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Women aged > 40 years and weighed >40kg who were undergoing major abdominal or pelvic surgery for diagnosed or suspected gynaecologic malignancy
Exclusion criteria	Pre-operative VTE; hypersensitivity to enoxaparin / heparin / heparin derivatives; active bleeding and/or risk of bleeding; acute bacterial endocarditis; renal dysfunction of estimated glomerular filtration rate < 40ml/min/1.73m^2; severe liver dysfunction; previous history of thrombosis and/or thrombophilia and/or current use of anticoagulant, platelet aggregation inhibitor, salicylic acid derivative or thrombolytic drug
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Enoxaparin 60.5 (10.7) vs. IPC alone 53.2 (10.9); p=0.08. Gender (M:F): 35 female patients. Ethnicity: Implicitly assumed to be all Japanese
Further population details	1. Active cancer: Active cancer (Uterine corpus cancer 43.3%; Ovarian cancer 40%; Cervical cancer 13.3%; Other cancer

	3.3%). 2. Acute/elective: Elective 3. BMI : Obese (BMI over 30 kg/m2) (Obesity (BMI > 25) in enoxaprin group 31.3% vs. IPC alone group 7.1%; p=0.18). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Renal dysfunction (eGFR < 40ml/min/1.73m²) was a criterion for exclusion).
Indirectness of population	Serious indirectness: The participants are implicitly assumed to be all Japanese. Risk of developing VTE and incidence of VTE are lower amongst Asian populations compared to other populations.
Interventions	(n=16) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous injections 20mg every 12 hrs; started on post-operative day 2. Duration 7 days. Concurrent medication/care: All patients used IPC immediately prior to surgery and the enoxaparin group continued its use until the first enoxaparin injection. Indirectness: No indirectness (n=14) Intervention 2: Intermittent pneumatic compression devices - Below knee. Pre-surgery: IPC only applied to feet and ankles (Novamedix A-V Impulse System). Post-surgery: IPC applied to all areas below knees (Veno Stream, Terumo Corporation). Duration Until full ambulation. Concurrent medication/care: All patients used IPC immediately prior to surgery. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN versus IPC ALONE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: Incidence of DVT at Between 9 and 11 days after surgery; Group 1: 1/16, Group 2: 3/14; Comments: RR 3.43 (95% CI 0.40 to 29.33); p=0.32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Incidence of PE at Between 9 and 11 days after surgery; Group 1: 0/15, Group 2: 3/14; Comments: RR 7.47 (95% CI 0.42 to 132.78); p=0.10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: One case was excluded from the analyses related to PE because PE was not evaluated

due to the participant's allergy to the contrast medium so ultrasound was used only to evaluate DVT.; Group 2 Number missing: 0 Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Clinically apparent bleeding events at Between 9 and 11 days after surgery; Group 1: 2/16, Group 2: 1/14; Comments: p=1.0 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Defined as one or more of the following events: RBC transfusion of > 2units; a decrease in Hb conc. of > 2g/dl; intracranial/intraocular/GI/epidural haemorrhage; bleeding from wounds/abdomen/retroperitoneal cavity that required surgical treatment which occurred after the timing of the 1st injection of enoxaparin; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Nicolaides 1983[238]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Stratified into 4 groups according to the risk of DVT
Inclusion criteria	Over the age of 30 years, undergoing major abdominal operations
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): ECS group: 59.2 (16.6), UFH group: 58.6 (13.3), mechanical group: 57.3 (13.4). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Mixed 37.3% malignancy). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Electrical stimulation. Electrical calf stimulation applied as soon as the patient was anethetised and continued throughout the operation. Duration During operation only . Concurrent medication/care: Additional prophylactic measures were not used in the postoperative period. Indirectness: No indirectness (n=50) Intervention 2: Intermittent pneumatic compression devices - Full leg. Intermittent sequential compression of the legs, used continually during operation and for a minimum of 72 hours in the postoperative period. If after this time the patient was ambulant, the IPCD was discontinued and TED stockings were applied on both legs. These were worn continuously for the rest of the patients stay in hospital. The maximum period of continuous use was 2 weeks. Duration Until discharge. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=50) Intervention 3: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U subcutaneous heparin administered 2 hours before operation and then every 12 hours until discharge. Duration Until discharge. Concurrent medication/care: Not reported. Indirectness: No indirectness

Funding	Equipment / drugs provided by industry (Berk Pharmaceuticals UK provided the heparin, the Research Division of Kendall Corporation provided the intermittent sequential compression devices and TED stockings, and the A. G. Leventis Foundation provided a research grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ELECTRICAL STIMULATION versus FULL LEG Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 12/50, Group 2: 3/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Gender not reported, BMI not reported ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ELECTRICAL STIMULATION versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 12/50, Group 2: 7/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Gender not reported, BMI not reported ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus FULL LEG Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 7/50, Group 2: 3/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Gender not reported, BMI not reported ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT

	scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Nurmohamed 1995[242]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1471)
Countries and setting	Conducted in Multiple countries; Setting: 20 centres
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major general surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over the age of 40 years if they underwent major general surgery lasting more than 45 minutes
Exclusion criteria	Allergy for heparin, iodine or contrast material, document bleeding tendency, pregnancy and the use of drugs interfering with coagulation
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): UFH group: 61 (11), LMWH group: 61 (11). Gender (M:F): 670:734. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (35.8% cancer). 2. Acute/elective: Not applicable 3. BMI : Mixed (35.9% obese). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=725) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 20mg administered for 10 days or until discharge, starting 2 hours preoperatively. Duration 10 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=719) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U three times daily started 2 hours preoperatively for 10 days. Duration 10 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge

	- Actual outcome: All-cause mortality at Not reported; Group 1: 4/718, Group 2: 6/709 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 10 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 10 days; Group 1: 25/718, Group 2: 8/709 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 10 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 0/718, Group 2: 0/709 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 10 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Not reported; Group 1: 11/725, Group 2: 18/719 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 10 Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at Not reported; Group 1: 1/718, Group 2: 0/709 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 10
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Ockelford 1989[244]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=197)
Countries and setting	Conducted in New Zealand; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 42 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	More than 40 years of age, had a major abdominal surgery procedure exceeding 30 minutes, and an expected hospital stay of greater than 5 days
Exclusion criteria	Patients with a past history of a multiple VTE, concurrent antiplatelet or anticoagulant medication, significant renal failure and active peptic ulceration
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 64.8 (21.1), placebo group: 64.3 (12.4. Gender (M:F): 1:1.04 LMWH, 1:1.5 placebo. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (43% cancer). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable (Excluded renal failure).
Indirectness of population	No indirectness

Interventions	(n=102) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Fragmin 2500U administered 1-2 hours preoperatively and then once daily for 5-9 days. Duration 5-9 days. Concurrent medication/care: Not reported (n=95) Intervention 2: No treatment - Placebo. Normal saline solution. Duration 5-9 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Financial support provided by Kabi Vitrum AB, Stockholm)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 42 days; Group 1: 0/95, Group 2: 2/88
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 42 days; Group 1: 4/95, Group 2: 14/88
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 42 days; Group 1: 0/95, Group 2: 2/88
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 42 days; Group 1: 4/95, Group 2: 4/88
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7 Protocol outcome 5: Heparin-induced thrombocytopenia at duration of study - Actual outcome: Thrombocytopenia at 42 days; Group 1: 0/95, Group 2: 0/88 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Technical complications of mechanical interventions at duration of study;

Study	Onarheim 1986[245]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=52)
Countries and setting	Conducted in Norway; Setting: Not reproted
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Surgical treatment of gastric, colonic or rectal malignancy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >40 years, no contraindication to heparin treatment or hypersensitivity to iodine, no preceding anticoagulant medication, and informed consent
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH group: 70.7 (8.9), UFH group: 70.0 (8.9). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1.250 units once daily - 5.000 units

	twice daily). KABI 2165 5000U given subcutaneously starting 2 hours before surgery and then every morning for 6 days. Duration 6 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=27) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Heparin 5000U given subcutaneously starting 2 hours before surgery, then at 8pm on the day of operation and later twice daily for the following 6 days. Duration 6 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Other (KabiVitrum made the study possible)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 30 days; Group 1: 0/25, Group 2: 0/27
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some factors not reported e.g. gender; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 30 days; Group 1: 1/25, Group 2: 0/27
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some factors not reported e.g. gender; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 30 days; Group 1: 0/25, Group 2: 0/27
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Method of confirmation not reported; Baseline details: Some factors not reported e.g. gender; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening

clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 30 days; Group 1: 1/25, Group 2: 1/27 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some factors not reported e.g. gender; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Osman 2007[246]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Egypt; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Live donor renal transplant
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Live donor renal transplant patients
Exclusion criteria	Younger than 16 years, grafts with multiple arteries, a history of thromboembolic disease, atheromatous arteris, collagen vascular disease, intraoperative technical difficulties
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - --: Control group: 26 (6), LMWH group: 28.3 (8), UFH group: 29.4 (8). Gender (M:F): 52:23. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Open surgery 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Low molecular weight heparin (licensed in UK) - Tinzaparin (2,500 units once daily – 9,000 units

	once daily). Subcutaneous tinzaparin sodium once daily 3500U, started postoperatively. Duration 1 week. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=25) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Subcutaneous conventional UFH 5000U twice daily, started postoperatively . Duration 1 week. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=25) Intervention 3: No treatment - Usual care. No heparinisation. No further details. Duration 1 week. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TINZAPARIN (2,500 UNITS ONCE DAILY – 9,000 UNITS ONCE DAILY) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 2 weeks; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 2 weeks; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 2 weeks; Group 1: 1/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TINZAPARIN (2,500 UNITS ONCE DAILY – 9,000 UNITS ONCE DAILY) versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 2 weeks; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 2 weeks; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 2 weeks; Group 1: 1/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus USUAL CARE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 2 weeks; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 2 weeks; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 2 weeks; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Porteous 1989[265]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 40 years of age undergoing major abdominal surgery
Exclusion criteria	Patients with varicose veins, a past history of DVT or myocardial infarction, premenopausal females, and patients undergoing peripheral vascular surgery
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Above knee group: 68 (11), below knee group: 63.5 (11.2). Gender (M:F): 49:65. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (Malignant disease 40.4%). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness

Interventions	(n=60) Intervention 1: Anti-embolism stockings - Above knee. Above knee stockings fitted on the morning of operation, worn until discharge. Duration Until discharge. Concurrent medication/care: No other form of VTE prophylaxis was used, but leg movement in bed was encouraged and early mobilisation was routine. Indirectness: No indirectness (n=64) Intervention 2: Anti-embolism stockings - Below knee. Below knee stockings fitted on the morning of operation, worn until discharge. Duration Until discharge. Concurrent medication/care: No other form of VTE prophylaxis was used, but leg movement in bed was encouraged and early mobilisation was routine. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Stockings and I-labelled fibrinogen provided by Brevet Hospital Products LTD)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABOVE KNEE versus BELOW KNEE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 3/56, Group 2: 1/58 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 6	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Rasmussen 1988[270]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=248)
Countries and setting	Conducted in Denmark; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted for major abdominal surgery (duration of anaesthesia more than 1 hour and of age more than 40 years)
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): AES group: 63 (41-87), UFH group: 62 (40-90), AES+UFH: 61 (40-87). Gender (M:F): 109:139. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Mixed (60% obesity (not defined)). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness

Interventions	(n=74) Intervention 1: Anti-embolism stockings - Below knee. Bilateral AES from the toes to the knee were applied from the evening for operation to complete mobilisation, or for not less than 5 days postoperatively. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=85) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Sodium heparin 5000U administered subcutaneously every 12 hours beginnings on the evening before operation and continued to complete mobilisation or for not less than 5 days postoperatively. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=89) Intervention 3: Anti-embolism stockings - Below knee. AES below knee + UFH 5000U. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (The 99mTc-labelled plasmin and a Novo thrombograph was provided by Novo Ltd and Novo diagnostics)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Not reported; Group 1: 0/74, Group 2: 0/85
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Not reported; Group 1: 0/74, Group 2: 0/85
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at Not reported; Group 1: 0/74, Group 2: 0/85
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE + UFH versus BELOW KNEE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Not reported; Group 1: 0/89, Group 2: 0/74
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Not reported; Group 1: 0/89, Group 2: 0/74
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at Not reported; Group 1: 0/89, Group 2: 0/74
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE + UFH versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Not reported; Group 1: 0/89, Group 2: 0/85
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at Not reported; Group 1: 0/89, Group 2: 0/85
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Not reported; Group 1: 0/89, Group 2: 0/85 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Rasmussen 2006[271]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=427)
Countries and setting	Conducted in Denmark, Norway; Setting: University and large community hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	Hospitalised for major abdominal surgery, gave written informed consent, and were over 18 years old. Surgery was more than 1 hour
Exclusion criteria	Severe peripheral arterial insufficiency (absence of a palpable pulsation in the dorsalis pedis artery), pregnancy, allergy to radiographic contrast medium, acid sulfite or LMWH, hepatic insufficiency, acute stroke within the last 3 months, gastrointestinal bleeding within the last month, hemorrhagic diathesis, anticoagulation treatment, treatment with dectran, psychosis or severe dementia, simultaneous participation in another clinical study or previous participation in the present study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): Standard duration group: 67 (22-93), extended duration group: 67 (25-91). Gender (M:F): 174:169. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable

Indirectness of population	No indirectness
Interventions	(n=222) Intervention 1: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin 5000U once daily and AES for 7 days. The first dose was administered on the evening prior to surgery, or a reduced dose of 2500U was administered 2 hours prior to surgery and repeated 12 hours later. Patients were randomised to receive no further treatment. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=205) Intervention 2: Low molecular weight heparin (licensed in UK) - Dalteparin (1,250 units once daily - 5,000 units twice daily). Dalteparin 5000U once daily and AES for 7 days. The first dose was administered on the evening prior to surgery, or a reduced dose of 2500U was administered 2 hours prior to surgery and repeated 12 hours later. Patients were randomised to receive treatment for a further 28 days. Duration 28 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Supported by grants from Pfizer Global Pharmaceuticals, the Apoteker Foundation of 1991, the Foundation of 1870, Nycomed Denmark, the Lily Benthine Lunds Foundation, the J and L Boserups Foundation, the Beckett Foundation, the S and I Hansens Foundation, the TM Hansen Foundation and the Else and Mogens Wedell-Wedellsborgs Foundation, Denmark)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DALTEPARIN STANDARD DURATION (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) + AES versus DALTEPARIN EXTENDED DURATION (1,250 UNITS ONCE DAILY - 5,000 UNITS TWICE DAILY) + AES

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 3 months; Group 1: 17/222, Group 2: 20/205
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 28 days; Group 1: 26/178, Group 2: 12/165
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 44; Group 2 Number missing: 40

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 2 months; Group 1: 3/178, Group 2: 0/165 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 44; Group 2 Number missing: 40 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 2 months; Group 1: 4/222, Group 2: 1/205 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 28 days; Group 1: 0/222, Group 2: 0/205 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Sakon 2010[280]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Japan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Abdominal cancer surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female patients were eligible if they were >40 years old and were undergoing a planned, curative laparotomy for cancer of >45 minutes duration. Abdominal cancer surgery was defined as including all intrapelvic and upper intra-abdominal operations between the diaphragm and the pelvic floor. Only patients with a life expectancy of 6 months of more after surgery were considered for study enrollment
Exclusion criteria	Patients were excluded if the only received surgery under laparascopy or other endoscopic conditions, had a hypersensitivity to heparin or thrombocytopenia due to heparin, had clinical signs of DVT at screening or evidence of thromboembolic disease within 1 year before surgery, or had received systemic chemotherapy within 3 weeks before study drug initiation. Women of childbearing potential and those who were pregnant or lactating were also excluded.
Age, gender and ethnicity	Age - Mean (SD): LMWH + IPCD group: 67.7 (10.1), IPCD group: 66.1 (10.1). Gender (M:F): 69:45. Ethnicity: Not reported
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Not applicable 3. BMI : Mixed (21% obese (>25 BMI)). 4. Laparoscopic/open surgery: Open surgery 5. Renal impairment: Not applicable
Indirectness of population	No indirectness

Interventions	(n=113) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Subcutaneous injection of enoxaparin 20mg twice daily, started 24-36 hours after surgery and continued for 14 days. All patients received at least one course of post surgical IPCD before administration of the first enoxaparin dose. Duration 14 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=38) Intervention 2: Intermittent pneumatic compression devices - Mixed full leg/below knee. IPCD prophylaxis alone. Length not reported. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Financially supported by sanofi-aventis K K, Japan)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) + IPCD versus MIXED FULL LEG/BELOW KNEE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 14 days; Group 1: 1/83, Group 2: 6/31
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 7

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 14 days; Group 1: 0/83, Group 2: 0/31
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 7

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Major bleeding at 14 days; Group 1: 5/109, Group 2: 1/38
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 0

Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Scurr 1981[292]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over the age of 40 who were about to undergo major abdominal surgery
Exclusion criteria	Patients with a history of DVT or PE
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Foot pump: 57.3 (40-82), control: 57.8 (40-83). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (77% malignancy). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Foot pumps or foot impulse devices - Foot pumps. Pedi-Pulsor, from the beginning of the procedure until the patient regained consciousness on the operating table. Duration Not reported. Concurrent medication/care: Not reported (n=33) Intervention 2: No treatment - Usual care. Control group, legs were immobile on the operating table. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOOT PUMPS versus USUAL CARE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at Not reported; Group 1: 0/33, Group 2: 1/33
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 6/33, Group 2: 15/33 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Soderdahl 1997[298]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major urological surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for major urological surgery
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Thigh length group: 64.8 (46-80), calf length group: 58.6 (24-77). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Intermittent pneumatic compression devices - Full leg, Thigh length IPCD individually fitted

	postoperatively, and compression applied before induction of anesthesia and continued at all times while the patient was in bed until fully ambulatory or hospital discharge. AES was not used. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=43) Intervention 2: Intermittent pneumatic compression devices - Below knee. Calf length IPCD individually fitted postoperatively, and compression applied before induction of anesthesia and continued at all times while the patient was in bed until fully ambulatory or hospital discharge. AES was not used. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FULL LEG versus BELOW KNEE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 3 months; Group 1: 0/47, Group 2: 1/43
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Not all factors reported; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 3 months; Group 1: 1/47, Group 2: 0/43
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Not all factors reported; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 3 months; Group 1: 0/47, Group 2: 1/43
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Not all factors reported; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge: Major bleeding. Meets one or more of the following

	criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Song 2014[299]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=220)
Countries and setting	Conducted in South Korea; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Gastric cancer patients undergoing surgery, patients with histologically proven adenocarcinoma through endoscopic biopsy
Exclusion criteria	History of PTE, or DVT in the previous 1 years, preoperative prolonged immobilisation or being wheelchair bound, diseases of bleeding tendency, major surgery in the previous 6 months, cerebrovascular accident in the previous 3 months, uncontrolled hypertension, congestive cardiac failure, renal or liver impairment, allergy to heparin or heparin induced thrombocytopenia, varicose veins or chronic venous insufficiency, previous chemotherapy, radiotherapy, anticoagulation therapy, transfusion, BMI <18.5kg/m², pregnancy or plan to become pregnant
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): LMWH + IPCD group: 56.31 (11.15), IPCD group: 58.77 (9.67). Gender (M:F): 150:70. Ethnicity: Not reported
Further population details	1. Active cancer: Active cancer 2. Acute/elective: Not applicable 3. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI 23.76 (2.65)), 4. Laparoscopic/open surgery: Not applicable (47% laparoscopic, 53% open), 5. Renal impairment: No

	renal impairement (eGFR greater than 30ml/min/1.73m2) (Excluded renal impairment but not defined).
Indirectness of population	No indirectness
Interventions	(n=108) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin was administered at 24 hour intervals in a daily dose of 40mg, starting postoperatively. IPCD (length not reported) was initiated preoperatively and continued until postoperative discharge. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=112) Intervention 2: Intermittent pneumatic compression devices - Mixed full leg/below knee. IPCD (length not reported) was initiated preoperatively and continued until postoperative discharge. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Covidien)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) + IPCD (UNDEFINED) versus MIXED FULL LEG/BELOW KNEE

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 30 days; Group 1: 0/109, Group 2: 3/112
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Overall 3 people excluded from analysis (1 had HIT, 1 withdrew consent, 1 underwent bypass surgery that led to noncurative operation); Group 2 Number missing: , Reason: Overall 3 people excluded from analysis (1 had HIT, 1 withdrew consent, 1 underwent bypass surgery that led to noncurative operation)

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 30 days; Group 1: 0/108, Group 2: 0/112
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Overall 3 people excluded from analysis (1 had HIT, 1 withdrew consent, 1 underwent bypass surgery that led to noncurative operation); Group 2 Number missing: , Reason: Overall 3 people excluded from analysis (1 had HIT, 1 withdrew consent, 1 underwent bypass surgery that led to noncurative operation)

Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 30 days; Group 1: 2/108, Group 2: 0/112 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Overall 3 people excluded from analysis (1 had HIT, 1 withdrew consent, 1 underwent bypass surgery that led to noncurative operation); Group 2 Number missing: , Reason: Overall 3 people excluded from analysis (1 had HIT, 1 withdrew consent, 1 underwent bypass surgery that led to noncurative operation)	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Strand 1975[306]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Denmark; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Gastrointestinal or urinary tract surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing surgery on the gastrointestinal or urinary tract and some undergoing other major surgery procedures
Exclusion criteria	Patients undergoing minor surgery, subjects less than 30 years old, patients with fractures, subjects suffering from either spontaneous or drug induced haemorrhagic diathesis, patients requiring acute surgical intervention, and patients with wound haematomas or superficial phlebitis of the lower extremities
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 31-90. Gender (M:F): 49:51. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (28% malignant disease). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness

Interventions	(n=50) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Heparin given subcutaneously every 12 hours, the first dose was given 1-3 hours before surgery and the last dose on the morning of the 7th postoperative day. Duration 7 days . Concurrent medication/care: All patients were subject to routine procedures of the department. Indirectness: No indirectness (n=50) Intervention 2: No treatment - Placebo. Placebo solution, every 12 hours, the first dose was given 1-3 hours before surgery and the last dose on the morning of the 7th postoperative day. Duration 7 days . Concurrent medication/care: All patients were subjected to the routine procedures of the department . Indirectness: No indirectness
Funding	Other (Supported by the heart foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 10 weeks ; Group 1: 3/50, Group 2: 10/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 10 participants dropped out but unclear which groups they were in ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 10 weeks ; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 10 participants dropped out but unclear which groups they were in ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 10 weeks ; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 10 participants dropped out but unclear which groups they were in ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number

missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Taberner 1978[310]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=145)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal or vaginal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Patients with a history of DVT
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): VKA group: 51.6, UFH group 52.4, placebo group: 50.3 SD not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (5.5% cancer). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Vitamin K antagonists - Acenocoumarol (all doses), 6mg nicoumalone initiated at least 5 days

	before surgery. The optimum preoperative prothrombin ratio was considered to be 2.0-2.5 using the BCT. Duration 14 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=49) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Twice daily doses of calcium heparin (Choay) 5000U subcutaneously, treatment began 2 hours preoperatively and continued for 7 days. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=48) Intervention 3: No treatment - Placebo. Saline subcutaneously twice daily beginning 2 hours preoperatively and continuing for 7 days. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Heparin supplied by Choay Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACENOCOUMAROL (ALL DOSES) versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 7 days; Group 1: 3/48, Group 2: 3/49
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACENOCOUMAROL (ALL DOSES) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 7 days; Group 1: 3/48, Group 2: 11/48
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge

- Actual outcome: DVT at 7 days; Group 1: 3/49, Group 2: 11/48 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Törngren 1978[314]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in Sweden; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention time: 6-8 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major gastrointestinal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with planned major gastrointestinal surgery
Exclusion criteria	Patients with a history of bleeding tendency, iodine allergy, age below 40 years and previous thyroid resections or hypothyroidism
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (range): UFH group: 66.1 (40-85), control group: 65.9 (40-83). Gender (M:F): 66:58. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (24% cancer). 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=66) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously),

	Calcium heparin 5000U given 12 hourly. Injections were given subcutaneously starting 2 hours before surgery and continuing for 6-8 days postoperatively . Duration 6-8 days. Concurrent medication/care: Not reported . Indirectness: No indirectness (n=62) Intervention 2: No treatment - Placebo. 5% glucose solution given 12 hourly. Injections were given subcutaneously starting 2 hours before surgery and continuing for 6-8 days postoperatively . Duration 6-8 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Supported by grants from Karolinska Institutet, Stockholm)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 6-8 days; Group 1: 1/63, Group 2: 2/61
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Allergic reaction, patient refused, discharged; Group 2 Number missing: 1, Reason: Not reported

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at Mean 10.5 days; Group 1: 10/63, Group 2: 20/61
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Allergic reaction, patient refused, discharged; Group 2 Number missing: 1, Reason: Not reported

Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 6-8 days; Group 1: 1/63, Group 2: 2/61
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Allergic reaction, patient refused, discharged; Group 2 Number missing: 1, Reason: Not reported

Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial,

intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 6-8 days; Group 1: 24/63, Group 2: 23/61 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Allergic reaction, patient refused, discharged; Group 2 Number missing: 1, Reason: Not reported Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 6-8 days; Group 1: 0/63, Group 2: 0/61 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Allergic reaction, patient refused, discharged; Group 2 Number missing: 1, Reason: Not reported	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Tsapogas 1971[315]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=95)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Patients who were to have operations on the lower limbs
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 56.1 (40-83). Gender (M:F): 93:2. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Anti-embolism stockings - Below knee. Prior to operation each patient was fitted with below knee AES used until discharge from hospital. Throughout the postoperative period, the foot of the bed was elevated 30

	degrees to reduce venous stasis. Early ambulation was encouraged. Passive and active dorsal and plantar flexion of the feet was started in the recovery room and continued for 5 minutes at 2 hour intervals throughout the day. Duration Until discharge. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=44) Intervention 2: No treatment - Usual care. None of the measures taken in the AES group were applied to the control group. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Other (Cutter Laboratories Inc, Berkeley, Calif, and A B Kabi, Stockholm provided the fibrinogen and plasminogen for the laboratory testing)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BELOW KNEE versus USUAL CARE Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 7 days; Group 1: 2/51, Group 2: 6/44 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Turner 1984[316]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=196)
Countries and setting	Conducted in United Kingdom; Setting: University of Bristol Department of Gynaecology
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Major gynecological surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients >35 years of age admitted for elective major gynaecological surgery
Exclusion criteria	Malignant disease, diabetic, pregnant, history of thromboembolism, or other indication for anticoagulant prophylaxis or therapy
Recruitment/selection of patients	All patients admitted
Age, gender and ethnicity	Age - Mean (SD): AES group: 47.6 (9.8), control 45.6 (9.4). Gender (M:F): Female. Ethnicity: Not reported
Further population details	1. Active cancer: No active cancer 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=104) Intervention 1: Anti-embolism stockings - Above knee. AES above knee. fitted on the day of admission and

	worn throughout their stay in hospital. Duration Not reported. Concurrent medication/care: The usual routine of physiotherapy to encourage early leg activity in bed and early ambulation was followed, but no other specific measures for preventing DVT were used. Indirectness: No indirectness (n=92) Intervention 2: No treatment - Usual care. No stockings. Duration Not reported. Concurrent medication/care: The usual routine of physiotherapy to encourage early leg activity in bed and early ambulation was followed, but no other specific measures for preventing DVT were used. Indirectness: No indirectness
Funding	Other (Stockings supplied by the Kendall Company Hospital Products Division)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABOVE KNEE versus USUAL CARE Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at Not reported; Group 1: 0/104, Group 2: 0/92 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 0/104, Group 2: 4/92 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 0/104, Group 2: 0/92 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital

	discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Turpie 2007[317]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1309)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 32 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over 40 years, weighing over 50kg and scheduled to undergo abdominal surgery expected to last longer than 45 minutes
Exclusion criteria	Patients due to undergo vascular surgery, with evidence of leg ischemia caused by peripheral vascular disease, or unable to receivce intermittent pneumatic compression or elastic stockings, pregnant women and women of childbearing age not using effective contraception, life expectancy < 6 months, clinical signs of DVT and/or history of VTE within the previous 3 months, active bleeding, documented congenital or acquired bleeding disorder, active ulcerative gastrointestinal disease unless it was the reason for surgery, hemorrhagic stroke or surgery on the brain, spine or eyes within the previous 3 months, bacterial endocarditis or other contraindication for anticoagulant therapy, planned indwelling intrathecal or epidural catheter for more than 6 hours after surgical closure, unusual difficulty in achieving epidural or spinal anesthesia, known hypersensitivity to fondaparinux or iodinated contrast medium, current addictive disorders, serum creatinine concentration above 2.0mg dL-1 in a well hydrated patient and platelet count below 100 000mm-3, patients requiring anticoagulant therapy, or other pharmacologic prophylaxis besides IPC according to the investigator
Recruitment/selection of patients	Not reported

Age, gender and ethnicity	Age - Mean (SD): Fondaparinux group: 60 (40-93), placebo group: 59 (40-95). Gender (M:F): 635:650. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (38.8% cancer). 2. Acute/elective: Not applicable 3. BMI : Mixed (41% obese (men BMI >30kgm-2, women BMI 28.6kg m-2)). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Mixed (1% creatinine clearance <30mL min-1).
Indirectness of population	No indirectness
Interventions	(n=650) Intervention 1: Fondaparinux - Fondaparinux (all doses). Fondaparinux 2.5mg, starting 6-8 hours after surgical closure. During the onstudy drug period of 5-9 days, all patients recieved IPCD using any type of device except a foot pump, for a duration left to the investigators discretion. The use of elastic stockings was left to the investigators discretion . Duration 5-9 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=659) Intervention 2: Intermittent pneumatic compression devices - Mixed full leg/below knee. Placebo + IPCD. During the onstudy drug period of 5-9 days, all patients recieved IPCD (length not reported) using any type of device except a foot pump, for a duration left to the investigators discretion. The use of elastic stockings was left to the investigators discretion . Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Funded by Sanofi-Synthelabo and then GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX (ALL DOSES) + IPCD versus MIXED FULL LEG/BELOW KNEE (+ PLACEBO)

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 32 days; Group 1: 8/635, Group 2: 5/650
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 9

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 32 days; Group 1: 7/424, Group 2: 22/418

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 226; Group 2 Number missing: 241 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 32 days; Group 1: 1/424, Group 2: 3/418 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 226; Group 2 Number missing: 241 Protocol outcome 4: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at 32 days; Group 1: 10/635, Group 2: 1/650 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 9 Protocol outcome 5: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge - Actual outcome: Fatal PE at 32 days; Group 1: 1/635, Group 2: 1/650 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 226; Group 2 Number missing: 241	
Protocol outcomes not reported by the study	Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Van vroonhoven 1974[325]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Netherlands; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Elective general surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over 40 years admitted to hospital for an elective general surgical procedure
Exclusion criteria	Patients already on oral anticoagulants and patients undergoing vascular or thyroid surgery
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 40-80+. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable (18% cancer). 2. Acute/elective: Elective 3. BMI : Mixed (20% obesity (not defined)). 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Vitamin K antagonists - Acenocoumarol (all doses). Acenocoumarol (nicoumalone, 'Sintrom') by mouth. Started as soon after the operation as possible, usually on the evening after the operation or on the first post operative day. The dose was regulated according to the results of daily thrombotests, the aim was a thrombotest value of 5-10% of normal. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=50) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Subcutaneous injection of calcium heparin 2 hours before the operation and 12 hourly thereafter for 8 days. Duration 8 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Choay Pharmaceuticals supplied Calciparin)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus ACENOCOUMAROL (ALL DOSES)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler)

ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at Not reported; Group 1: 1/50, Group 2: 9/50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge - Actual outcome: Major bleeding at Not reported; Group 1: 0/50, Group 2: 0/50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Vandendris 1980[326]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Belgium; Setting: Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: 6 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Open prostatectomy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients having open prostatectomy performed under general anesthesia and required at least 7 days of hospital stay
Exclusion criteria	Patients with thyroid disease, recent VTE or lower limp amputation, and patients taking anticoagulants or antiagregating drugs
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): UFH group: 72.2, placebo group: 70.0. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Not applicable 3. BMI : Not applicable 4. Laparoscopic/open surgery: Open surgery 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). Calcium heparin 5000U, given 2 hours before operation and then every 8 hours for 6 days. Duration 6 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=33) Intervention 2: No treatment - Placebo. 0.2ml distilled water subcutaneous injection, given 2 hours before operation and then every 8 hours for 6 days. Duration 6 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY) versus PLACEBO

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge

- Actual outcome: DVT at Not reported; Group 1: 3/31, Group 2: 13/33 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at Not reported; Group 1: 0/31, Group 2: 0/33 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Wille-jørgensen 1985[337]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=196)
Countries and setting	Conducted in Denmark; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Elective major abdominal surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for elective major abdominal surgery provided they fulfilled one of the following criteria: age above 39, malignancy suspected, weight more than 19% above normal, varicose veins of the lower extremities, diabetes mellitus, hypertension, previous thromboembolism or cardiac failure
Exclusion criteria	Hepatic disease with coagulation factors II, VII and X below 40%, anticoagulation treatment, a history of peripheral arterial insufficiency and allergy to iodine
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): AES + UFH group: 61 (36-90), UFH group: 59 (40-87). Gender (M:F): 105:71. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Elective 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=94) Intervention 1: Anti-embolism stockings - Above knee. Thigh length AES fitted on both legs before surgery and used day and night during the observation period. UFH 5000U was administered twice daily subcutaneously, starting one hour preoperatively and continued for 7 days or until discharge. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=102) Intervention 2: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). UFH 5000U was administered twice daily subcutaneously, starting one hour preoperatively and continued for 7 days or until discharge. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Heparin and stockings were supplied by Novo and Kendall. A Novo thrombography was supplied by Novo Diagnostics)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABOVE KNEE + UFH versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED SUBCUTANEOUSLY)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT at 7 days; Group 1: 1/86, Group 2: 7/90
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 12

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: PE at 7 days; Group 1: 2/86, Group 2: 6/90
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 12

Protocol outcome 3: Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge
- Actual outcome: Fatal PE at 7 days; Group 1: 0/86, Group 2: 1/90
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 12

Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	Wille-jorgensen 1991[336]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=178)
Countries and setting	Conducted in Denmark; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Acute abdominal operations
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing acute abdominal operations, provided they fulfilled at least one of these risk factors: more than 39 years of age, malignant lesions suspected, varicose veins, cardiac disease or hypertension, diabetes mellitus, obesity or earlier thromboembolic episodes. The operation had to be considered to last for more than 1 hour
Exclusion criteria	Allergy to iodine, dextran or heparin use, hepatic or untreated cardiac failure, severe peripheral arterial insufficiency, pregnancy or bleeding in the gastrointestinal tract
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): AES + UFH group: 72 (40-95), UFH group: 70.7 (37-91). Gender (M:F): 58:102. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Acute/elective: Acute 3. BMI : Not applicable 4. Laparoscopic/open surgery: Not applicable 5. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: Unfractionated heparin - Unfractionated heparin (low dose, administered subcutaneously). 5000U sodium heparin administered subcutaneously preoperatively and continued twice daily for 7 days or until the patient was fully mobile. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=94) Intervention 2: Anti-embolism stockings - Above knee. Thigh length AES plus 5000U sodium heparin were given in combination. AES were applied preoperatively and worn day and night until full mobilisation occured. Duration 7 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Supported in part by grants from NOVO A/S Kabi Vitrum A/S and the Kendall Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABOVE KNEE + UFH versus UNFRACTIONATED HEPARIN (LOW DOSE, ADMINISTERED

SUBCUTANEOUSLY) Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge - Actual outcome: All-cause mortality at 30 days; Group 1: 16/79, Group 2: 11/81 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 3 Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT at 30 days; Group 1: 2/79, Group 2: 12/81 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 3 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 30 days; Group 1: 0/79, Group 2: 0/81 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

H.33 Bariatric surgery

Study	Imberti 2014[154]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=250)
Countries and setting	Conducted in Italy; Setting: Italian centres were eligible for inclusion
Line of therapy	Not applicable
Duration of study	Intervention time: 9±2 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by bilateral colour Doppler ultrasound of the lower limb venous system. PE: confirmed by perfusion lung scan matched with chest X-ray, ventilation/perfusion scan, computed tomography, angiography Major bleeding: defined as fatal bleeding, bleeding in vital organs (intracranial, intraspinal, retroperitoneal, intraarticular, pericardial, intraocular); bleeding at the surgical site requiring reoperation; and bleeding associated with a reduction in Hb of at least 2 g/dL or requiring transfusion of at least 2 units of packed red cells/whole blood. Bleeding was defined as clinically relevant if it was overt but did not meet the other criteria for major bleeding.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive morbidly obese patients aged >18 years with a BMI >36 kg/m2 who were scheduled to undergo open and laparoscopic primary or revisional bariatric surgery under general anaesthesia
Exclusion criteria	Presence of liver disease (acute and chronic hepatitis, cirrhosis, aminotransferases >3 times the normal upper limit); kidney disease (creatinine levels >1.2 mg/dL); platelet count <100,000/mm3; documented history of DVT/PE in the last 6 months; documented congenital/acquired coagulation disorders; concomitant anticoagulant/antiplatelet therapy for other risk factors; known hypersensitivity to heparin and derivatives; pregnancy; previous heparin-induced thrombocytopenia; active peptic ulcer or known angiodysplasia of the colon, severe uncontrolled hypertension (systolic blood pressure ≥200 mmHg, diastolic ≥110 mmHg); previous haemorrhagic stroke, recent brain surgery (<3 months from randomization), recent major bleeding (<3 months of randomization), poor adherence to the study, withdrawal of informed consent; and participation in another clinical trial within the last 4 weeks or during the current trial.
Recruitment/selection of patients	Between April 2004 and February 2012, 258 consecutive morbidly obese patients (BMI >36) undergoing bariatric surgery were enrolled in this study
Age, gender and ethnicity	Age - Mean (range): 40.9 (18-64) years. Gender (M:F): 1/4. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Renal impairment: Not applicable

Extra comments	Type of surgery: laparoscopic gastric bypass 68%, laparoscopic sleeve gastrectomy 8.8%, laparoscopic gastric banding 8.4%, biliopancreatic diversion 9.6%, vertical gastroplasty 0.4%). BMI (mean (SD)): 6400IU group 44.2 (5.4), 44.6 (5.4) 4250IU group; operating time: 6400IU group 187 minutes, 4250IU group 176 minutes
Indirectness of population	No indirectness
Interventions	(n=119) Intervention 1: Low molecular weight heparin (not licensed in UK) - Parnaparin (3200 units once daily - 4250 units once daily). 6,400 IU/day (group B) of subcutaneous parnaparin starting 12 h preoperatively was administered. The second dose 24 h later and in any case at least 6 h after the closure of the surgical wound, once adequate hemostasis has been achieved. Subsequent injections were performed once a day for a period of 9 ± 2 days. Where the patient was discharged prior to completion of the treatment, the treatment was completed at home. Duration mean 14 days. Concurrent medication/care: Patients were recommended to use graduated compression stockings and intermittent pneumatic compression; early deambulation was strongly encouraged. Patients who received heparin + IPCD + AES + early deambulation: 62.2%. Indirectness: Serious indirectness (n=131) Intervention 2: Low molecular weight heparin (not licensed in UK) - Parnaparin (3200 units once daily - 4250 units once daily). 4,250 IU/day (group B) of subcutaneous parnaparin (Alfa Wassermann, Bologna, Italy) starting 12 h preoperatively, the second dose 24 h later and in any case at least 6 h after the closure of the surgical wound, once adequate hemostasis has been achieved. Subsequent injections were performed once a day for a period of 9 ± 2 days. Where the patient was discharged prior to completion of the treatment, the treatment was completed at home. Duration mean 14 days. Concurrent medication/care: Patients were recommended to use graduated compression stockings and intermittent pneumatic compression; early deambulation was strongly encouraged. Patients who received heparin + IPCD + AES + early deambulation: 58%. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARNAPARIN (6400IU/DAY) + IPCD + AES versus PARNAPARIN (4250IU/DAY) + IPCD + AES

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: All-cause mortality at 90 days; Group 1: 0/119, Group 2: 0/131
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic) at 11 days; Group 1: 1/119, Group 2: 1/131

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge - Actual outcome: PE at 11 days; Group 1: 0/119, Group 2: 1/131 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Heparin-induced thrombocytopenia at duration of study - Actual outcome: Heparin-induced thrombocytopenia at 11 days; Group 1: 1/119, Group 2: 1/131 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Technical complications of mechanical interventions at duration of study;

Study	**Kalfarentzos 2001[168]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Greece; Setting: University Hospital of Patras, Patras, Greece
Line of therapy	Not applicable
Duration of study	Intervention time: Until discharge

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DVT (symptomatic and asymptomatic): confirmed by compression ultrasonography (Doppler) Major bleeding: defined as haemorrphage associated with a decrease in haemoglobin levels of >2 g per decilitre or an episode requiring transfusion of >2 units of blood.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients aged >18 years, presenting with clinical morbid obesity (with a BMI >36) scheduled to undergo RYGBP12 were eligible.
Exclusion criteria	Pregnancy, active clinically significant bleeding, recent gastrointestinal bleeding or documented congenital bleeding tendency/disorder(s); thrombocytopenia or a previous history of thrombocytopenia (platelet count below 100x 10x9/L; hepatic or renal dysfunction; uncontrolled hypertension (blood pressure ≥200 mmHg systolic and/or ≥110 mmHg diastolic); acute bacterial endocarditis or conditions with a poor prognosis unrelated to morbid obesity; a history of haemorrphagic stroke; recent (<3 months prior to randomisation) brain, spinal or ophthalmological surgery; or a known hypersensitivity to heparin or LMWH. Patients for whom anticoagulation therapy was contraindicated, and those who had, in the 90 days, participated in any other therapeutic study evaluating DVT prophylaxis
Recruitment/selection of patients	Patients enrolled from March 1999 to August 2000
Age, gender and ethnicity	Age - Mean (SD): 35 (11) years. Gender (M:F): 1/4. Ethnicity: Not reported
Further population details	1. Active cancer: Not applicable 2. Renal impairment: Not applicable
Extra comments	BMI (mean (SD)): 0.6ml nadroparin group 48.8 (8), 1.0ml nadroparin group 48.6 (7.3). Operating time: 0.6ml nadroparin group 185.6 minutes, 1.0ml nadroparin group 196.7 minutes.
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Low molecular weight heparin (not licensed in UK) - Nadroparin (2850 units once daily - up to 57 units/kg once daily). 9500IU (1.0ml) administered subcutaneously once pre-operatively and once daily postoperatively until the day of discharge (10.2 days). Duration Until discharge (10.2 days). Concurrent medication/care: Average weight (mean (SD)): 134.4 (26.3). No other drugs with effects on coagulation were permitted. Indirectness: Serious indirectness (n=30) Intervention 2: Low molecular weight heparin (not licensed in UK) - Nadroparin (2850 units once daily - up to 57 units/kg once daily). 5700IU (0.6ml) administered subcutaneously once pre-operatively and once daily postoperatively until the day of discharge (10.2 days). Duration Until discharge (mean 9.4 days). Concurrent medication/care: Average weight (mean (SD)): 131 (24). No other drugs with effects on coagulation were permitted. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NADROPARIN (ABOVE MAX. DOSE) versus NADROPARIN (HIGH DOSE) Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic and asymptomatic) at 90 days; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Major bleeding at Unclear; Group 1: 2/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at duration of study; Technical complications of mechanical interventions at duration of study;

Study	**EFFORT trial: Steele 2015[304]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=198)
Countries and setting	Conducted in USA; Setting: Academic institution that is accredited by the American College of Surgeons and ASMBS Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program
Line of therapy	Not applicable

Duration of study	Intervention + follow up: Intervention duration of hopsitalisation, follow up 10-14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years or over; BMI 35-59kg/m^2; undergoing laproscopic vertical sleeve gastrectomy or laproscopic Roux-en Y gastric bypass
Exclusion criteria	BMI >60; contraindications to LMWH or selective antithrombin III agonists; previous history of DVT or PE, documented clotting/coagulation disorders; history of treatment of cancer within last year; history of venous statis or superficial thrombophelebitis, vein stripping or ligatation, obesity hypoventilation syndrome; recent history of smoking (within last year)
Recruitment/selection of patients	Consecutive bariatric surgery patients from an academic institution from July 2010 to August 2013,
Age, gender and ethnicity	Age - Mean (SD): 41.1±9.6 (range 18-68). Gender (M:F): 32:166. Ethnicity: white non-hispanic 64.6%, black non-hispanic 32.3%, hispanic 2%
Further population details	1. Active cancer: No active cancer (Cancer 1.5%). 2. Renal impairment: Not stated
Extra comments	laproscopic vertical sleeve gastrectomy 37.9%; laproscopic Roux-en Y gastric bypass 62.1%
Indirectness of population	No indirectness
Interventions	(n=98) Intervention 1: Low molecular weight heparin (licensed in UK) - Enoxaparin (20mg once daily – 60mg twice daily). Enoxaparin 40mg 1x pre-op and 40mg x2 daily post-op, administered subcutaneously. Duration Until discharge, average length of stay 2.5 days. Concurrent medication/care: Sequential compression devices and antiembolic stockings 4-6 hours post-op, early mobilisation (n=100) Intervention 2: Fondaparinux - Fondaparinux (all doses). 5mg once daily post-operatively. Duration Until discharge, average length of stay 2.5 days. Concurrent medication/care: Sequential compression devices and antiembolic stockings 4-6 hours post-op, early mobilisation
Funding	Study funded by industry (GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN (20MG ONCE DAILY – 60MG TWICE DAILY) versus FONDAPARINUX (ALL DOSES)

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge
- Actual outcome: DVT (symptomatic and asymptomatic). confirmed by magnetic resonance venography at 14 days; Group 1: 2/83, Group 2: 2/94; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Heparin-induced thrombocytopenia at duration of study - Actual outcome: Thrombocytopenia at 14 days; Group 1: 0/83, Group 2: 1/94; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: DVT (symptomatic) at 7-90 days from hospital discharge - Actual outcome: DVT (symptomatic) at 14 days; Group 1: 2/98, Group 2: 2/100	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Technical complications of mechanical interventions at duration of study

H.34 Cardiac surgery

Study	**ATACAS trial: Myles 2016[234]**
Study type	RCT (Patient randomised; Parallel)

Study	ATACAS trial: Myles 2016[234]
Number of studies (number of participants)	1 (n=2100)
Countries and setting	Conducted in Australia, Canada, Hong Kong (China), Italy, New Zealand, United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Patients were assessed daily during their hospital stay and were contacted by telephone 30 days after surgery.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults at increased risk for major complications related to age or coexisting conditions and were about to undergo on-pump (with cardiopulmonary bypass) or off-pump (without cardiopulmonary bypass) coronary artery surgery, with or without cardiac-valve placement or another procedure. Patients were eligible if they had not been taking aspirin regularly before the trial or had stopped taking aspirin at least 4 days before CABG surgery.
Exclusion criteria	Poor English language comprehension. Clinician preference for antifibrinolytic therapy. Urgent surgery for unstable coronary syndromes where for clinical reasons antiplatelet medication cannot be discontinued. Active peptic ulceration. Allergy or contraindication to aspirin or tranexamic acid. Aspirin therapy within 4 days of surgery. Warfarin or clopidogrel therapy within 7 days of survery, or GIIb/IIIa antagonists within 24 hours of surgery. Thrombocytopenia or any other known history of bleeding disorder. Severe renal impairment (serum creatinine >250 micro mol/l or estimated creatinine clearance <25 ml/min). Recent hematuria. Thromboembolic disease relating to: history of postoperative or spontaneous pulmonary embolism, spontaneous arterial thrombosis or familial hypercoaguability (eg. lupus anticoagulant, protein C deficiency). Pregnancy.
Age, gender and ethnicity	Age - Mean (SD): Aspirin: 66.5 (9.7) Placebo: 66.2 (10.2) . Gender (M:F): Aspirin: 83.3% male, Placebo: 81.5%. Ethnicity: Not stated
Further population details	1. Active cancer: Not applicable 2. Antiplatelet therapy: Not applicable (Clopidogrel therapy within 7 days of surgery excluded, other antiplatelets not stated). 3. BMI : Mixed 4. Bowel surgery: Not applicable 5. Cardiac bypass:

Study	ATACAS trial: Myles 2016[234]
	Systematic review: mixed (Not Systematic review, but mixed population). 6. Renal impairment: Mixed
Extra comments	A. At risk of major complications defined by any of: Age ≥70 years. Left ventricular impairment (fractional area change <20%, ejection fraction <40%, or at least moderate impairment on ventriculography). Concomitant valvular or aortic surgery. Left ventricular aneurysmectomy. Repeat cardiac surgery ("re-do"). Chronic obstructive pulmonary disease. Renal impairment (se. creatinine >150 micromol/l or creatinine clearance <45 ml/min). Obesity (BMI >25 kg/m²). Pulmonary hypertension (mPAP >25 mmHg). Peripheral vascular disease.
Indirectness of population	No indirectness
Interventions	(n=1059) Intervention 1: Aspirin. 100mg aspirin administered 1 to 2 hours before surgery, with or without anxiolytic premedication. Duration Daily assessment during hospital stay and phone call 30 days after surgery. Concurrent medication/care: All patients received standard surgical and other perioperative care, including selection of vein and artery conduit harvesting, determination of the extent of grafting needed according to the results of coronary angiography, myocardial protection, surgical hemostatis, inotrope therapy, and postoperative care. There was no limitation to the use or postoperative aspirin or other antiplatelet therapy, and such therapy was administered in accordance with local practices. Indirectness: No indirectness (n=1068) Intervention 2: No treatment - Placebo. Matched placebo tablets 1 to 2 hours before surgery, with or without anxiolytic premedication. Duration Daily assessment during hospital stay and phone call 30 days after surgery. Concurrent medication/care: All patients received standard surgical and other perioperative care, including selection of vein and artery conduit harvesting, determination of the extent of grafting needed according to the results of coronary angiography, myocardial protection, surgical hemostatis, inotrope therapy, and postoperative care. There was no limitation to the use or postoperative aspirin or other antiplatelet therapy, and such therapy was administered in accordance with local practices. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Bayer Pharma provided the aspirin and matched placebo tablets. Other funding received from the Australian National Health and Medical research Council, the Australian and New Zealand

Study	ATACAS trial: Myles 2016[234]
	College of Anaesthetists and the National Institute of Health Research.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus PLACEBO

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome: Death at Within 30 days after surgery; Group 1: 14/1047, Group 2: 9/1053
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Postoperative therapy administered in accordance with local practices. ; Group 1 Number missing: 12, Reason: 6 withdrew consent, 4 had surgery cancelled, 2 underwent duplicate randomisation.; Group 2 Number missing: 15, Reason: 11 withdrew consent, 2 had surgery cancelled, 2 underwent duplicate randomisation.

Protocol outcome 2: Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge
- Actual outcome: Pulmonary embolism at Within 30 days after surgery; Group 1: 8/1047, Group 2: 10/1053
Indirectness of outcome: No indirectness ; Blinding details: Postoperative therapy administered in accordance with local practices. ; Group 1 Number missing: 12, Reason: 6 withdrew consent, 4 had surgery cancelled, 2 underwent duplicate randomisation.; Group 2 Number missing: 15, Reason: 11 withdrew consent, 2 had surgery cancelled, 2 underwent duplicate randomisation.
Protocol outcome 3: Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge
- Actual outcome: Reoperation for hemorrhage at Within 30 days after surgery; Group 1: 19/1047, Group 2: 22/1053
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Postoperative therapy administered in accordance with local practices. ; Group 1 Number missing: 12, Reason: 6 withdrew consent, 4 had surgery cancelled, 2 underwent duplicate randomisation.; Group 2 Number missing: 15, Reason: 11 withdrew consent, 2 had surgery cancelled, 2 underwent duplicate randomisation.

Protocol outcome 4: Major cardiac events at up to 90 days from hospital discharge
- Actual outcome: Myocardial infarction at Within 30 days after surgery; Group 1: 144/1047, Group 2: 166/1053
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Postoperative therapy administered in accordance with local practices. ; Group 1 Number missing: 12, Reason: 6 withdrew consent, 4 had surgery cancelled, 2 underwent duplicate randomisation.; Group 2 Number missing: 15, Reason: 11 withdrew consent, 2 had surgery cancelled, 2 underwent duplicate randomisation.
- Actual outcome: Stroke at Within 30 days after surgery; Group 1: 14/1047, Group 2: 12/1053
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Study	ATACAS trial: Myles 2016[234]
Indirectness of outcome: No indirectness ; Blinding details: Postoperative therapy administered in accordance with local practices. ; Group 1 Number missing: 12, Reason: 6 withdrew consent, 4 had surgery cancelled, 2 underwent duplicate randomisation.; Group 2 Number missing: 15, Reason: 11 withdrew consent, 2 had surgery cancelled, 2 underwent duplicate randomisation.	
Protocol outcomes not reported by the study	Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Goldhaber et al., 1995 [122]	RCT	1+	Total: 344 Intervention: n=172 Control: n= 172	Type of surgery: Coronary artery bypass. Duration: not reported. Intervention: Mean age: 63.2 ± 9.7 years M/F: 137/35 Control: Mean age: not reported M/F: 92/77 Pre-existing risk factors: Significantly greater proportion of patients in the	Type: Thigh-length IPCD device Dose: 30–45 mmHg Timing: First 98 patients started >24 hours post-operatively Patients 99 to 344 begun 4–12 hours post-surgery. Appeared to be worn until discharge Additional non-	Graduated compression stocking (length unknown). Appears to be begun immediately post-op. Aspirin 325 mg/day (unless contra-indicated)	Both groups: followed up until discharge	DVT Confirmed by: bilateral Doppler ultrasound on or after 4 post-op day	Intervention: 31/164 Control: 36/166 p value: 0.62	Comments: 14 participants dropped out after randomisation (8 IPCD + AES; and 6 AES). First 98 patients enrolled had delayed initiation of prophylaxis (outcome for these patients were not significantly different). Any interruption of prophylaxis > 3 hours was recorded. Significantly more non-compliance in the IPCD
								Proximal DVT Confirmed by: As above	Intervention: 5/164 Control: 6/166 p value: 0.98	
								PE Not routinely screened for. Non-fatal PE in control group confirmed by high probability V/Q scan	Intervention: 1/164 Control: 1/166 p value: 1.0000	

				comparison group had cancer	comparative prophylaxis: Graduated compression stocking (length unknown). Appears to be begun immediately post-op. Aspirin 325 mg/day (unless contra-indicated)			Fatal PE Confirmed by: clinical evaluation (presumably). Patient underwent pulmonary emo-bolectomy procedure so diagnosis reliable	Intervention: 1 Control: 0/166 Patient had not received the intervention and is not included in any other analysis as no DVT measure had been obtained. (therefore 1/165)	group. Difference between groups still not significant when analysed with only those whose compliance had not been interrupted. Age was a significant predictor of DVT. Not reported: PTS, QoL, bleeding Funding: not reported
								Survival	Intervention: 2/164 Control: 0/166 p value: 0.2462	
								Length of hospital stay	Intervention: Median 9 Control: Median 9 p value: 0.36 Not significant	

Study	**Kolluri 2016[177]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)

Study	Kolluri 2016[177]
Countries and setting	Conducted in USA; Setting: Hospital - single centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: After discharge patients were contacted by phone or scheduled for follow-up at 25 to 35 days after CABG.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients who developed symptomatic DVT or VTE underwent DUS scan of the lower extremities.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients scheduled to undergo a first or repeat isolated CABG operation.
Exclusion criteria	Long-term anticoagulation with unfractionated or low-moelcular-weight heparin, coumadin or heparinoids. Contraindication to anticoagulation. Creatinine clearance <30 mL/min. Body weight <50kg. Presence of indwelling epidural catheter. Hepatic failure. Pregnant state. <6 months life expectancy. Platelet count <100,00/mm³. Whole blood hemoglobin concentraton <d g/dL. VTE documented within last 3 months. Acute bacterial endocarditis. Cerebral metastasis or abscess. History of heparin-induced thrombocytopenia. Presence of acute deep venous thrombosis on a preoperative duplex ultrasound of the lower extremities. Inability to undergo venous duplex of lower extremities. Inability to consent. REfusal by treating physician.
Recruitment/selection of patients	All patients scheduled to undergo a first or repeat isolated CABG operation were considered for enrollment. On the day of admission to the hospital, before undergoing CABG surgery, the patients were randomly assigned to receive subcutaneous injections of saline versus subcutaneous injections of 2.5mg fondaparinux.
Age, gender and ethnicity	Age - Mean (SD): Placebo: 62 (8.9) Fondaparinux: 64.4 (8.9). Gender (M:F): 57:21 (73% male). Ethnicity: Not reported

Study	Kolluri 2016[177]
Further population details	1. Active cancer: Not applicable 2. Antiplatelet therapy: Not applicable 3. BMI : Not applicable (Weight stated, but BMI unclear.). 4. Bowel surgery: Not applicable 5. Cardiac bypass: Cardiac bypass (All undergoing CABG). 6. Renal impairment: No renal impairement (eGFR greater than 30ml/min/1.73m2) (Creatine clearance <30 mL/min excluded).
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Fondaparinux. 2.5 mg subcutaneous injections of fondaparinux sodium daily, starting at a mean of 12 ± 2 hours after wound closure or in the morning of the first postoperative day. The second dose was administered at a mean of 24 ± 2 hours after the first dose, and the subsequent injections were administered once daily for 9 days or until discharge of the patient from the hospital. Duration 9 days, or until discharge, whichever happened first. Concurrent medication/care: Graduated compression stockings and/or intermittent pneumatic compression (mechanical antithrombotic prophylaxis). Indirectness: No indirectness (n=37) Intervention 2: No treatment - Placebo. Subcutaneous injections of isotonic saline on the same schedule as the intervention group. Duration 9 days or until discharge, whichever happened first. Concurrent medication/care: Graduated compression stockings and/or intermittent pneumatic compression (mechanical antithrombotic prophylaxis). Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Glaxo Smith Kline provided the study drug, further funding received from the American College of Phlebology Foundation educational grant.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX versus PLACEBO Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) at 7-90 days from hospital discharge - Actual outcome: Asymptomatic right peroneal DVT detected by DUS at At time of discharge; Group 1: 0/35, Group 2: 1/32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 2 withdrew consent. Others not stated.; Group 2 Number missing: 5, Reason: Not stated.	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Pulmonary embolism. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at 7-90 days from hospital discharge; Major bleeding. Meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of

Study	Kolluri 2016[177]
	≥2g/dl; a serious or life threatening clinical event at up to 45 days from hospital discharge; Fatal PE. Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy at up to 45 days from hospital discharge; Health-related quality of life (validated scores only) at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge; Major cardiac events at up to 90 days from hospital discharge;

H.35 Thoracic surgery

No relevant clinical studies were identified.

H.36 Vascular surgery

Study	Ayo 2017[11]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Undergoing endovascular ablation for great saphenous vein valvular incompetence
Stratum	People undergoing varicose vein surgery
Subgroup analysis within study	Not applicable

Inclusion criteria	Documented great saphenous vein reflux on venous duplex, CEAP disease, palpable pulse of ankle brachial index >0.9.
Exclusion criteria	Previous ipsilateral intervention, history of deep vein thrombosis, hypercoagulable state, concomitant phlebectomy, CEAP class 6 disease.
Recruitment/selection of patients	Eligible patients, 2009-2013, New York Langone Medical Centre
Age, gender and ethnicity	Age - Other: Mean (SD not reported): compression: 52; usual care 49 years. Gender (M:F): 20/65. Ethnicity: NR
Further population details	1. Active cancer: No active cancer 2. BMI : Not applicable 3. Open versus endovascular: Endovascular (Endovascular radiofrequency or laser ablation). 4. Renal impairment: Not applicable
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Anti-embolism stockings - Above knee. Post-procedural compression therapy using thigh-high compression stockings (30-40mmHg) for 24 hours post procedure and then daily during waking hours for 7 days. The procedure was endovenous radiofrequency or laser ablation of great saphenous vein for valvular incompetence. If the patient required bilateral treatment, this was done on a separate occasion and for the subsequent procedure they were assigned to the opposite group. Duration 7 days post-procedure. Concurrent medication/care: NR (did not assess post-procedural doses of pain relief or compliance to stocking use). Indirectness: Serious indirectness; Indirectness comment: Some people were included in the study twice if they required bilateral treatment (number of people = 70, number of cases = 85) (n=46) Intervention 2: No treatment - Usual care. Usual care was 24 hours of post-procedural bandages (no compression therapy). The procedure was endovenous radiofrequency or laser ablation of great saphenous vein for valvular incompetence. If the patient required bilateral treatment, this was done on a separate occasion and for the subsequent procedure they were assigned to the opposite group. Duration 24 hours post-procedure. Concurrent medication/care: NR (did not assess post-procedural doses of pain relief). Indirectness: Serious indirectness; Indirectness comment: Some people were included in the study twice if they required bilateral treatment (number of people = 70, number of cases = 85)
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMPRESSION STOCKINGS (ABOVE KNEE) versus USUAL CARE

Protocol outcome 1: Health-related quality of life at up to 90 days from hospital discharge
- Actual outcome for People undergoing varicose vein surgery: Venous clinical severity score (VCSS) at day 7; MD; -1.23 (SEM: 1.78), Comments: Only mean final values

reported for each group, along with the P value from a t-test. Therefore, the SEM was calculated for the mean difference.); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for People undergoing varicose vein surgery: Chronic venous insufficiency questionnaire (CIVIQ-2) at day 90; MD; 6.6 (SEM: 7.28), Comments: Only mean final values reported for each group, along with the P value from a t-test. Therefore, the SEM was calculated for the mean difference.); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: around 80% missing, Reason: loss to follow-up; Group 2 Number missing: around 80% missing, Reason: loss to follow-up	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge; Pulmonary embolism at 7-90 days from hospital discharge; Major bleeding at up to 45 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge;

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Collins 1988 (74 studies included – including Belch 1980[19] and Spebar 1981[301])	Systematic Review	1+	Total: 15598 Intervention: 8112 Control: 7486	Type of surgery: general, orthopaedic and urological.	UFH Dose: Subcutaneous and given perioperatively. Additional non-comparative prophylaxis:	No prophylaxis Additional non-comparative prophylaxis: AES: 8 studies Aspirin: 2 studies	Given for 2-16 days or until ambulatory or discharg	DVT confirmed by radiolabelled fibrinogen or scanning	Int: 436/3677 Cont: 922/3389 p value: 0.0000	Not reported: Funding, QoL, LoS or PTS. Event rates reported here are for all studies as published in
								PE	Int: 74/1840 Cont: 104/1837 p value: 0.0212	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
					AES: 8 studies Aspirin: 2 studies Dextran: 1 study IPCD: 1 study	Dextran: 1 study IPCD: 1 study	ed.	Major bleeds	Int: 168/4433 Cont: 110/4177 p value: 0.0027	the systematic review.
								Proximal DVT	Int: 54/1563 Cont: 114/1563 p value: 0.0000	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Farkas 1993 [99]	RCT	1+	Total: 233 Intervention: n = 122 Control: n = 111 269 patients randomised, 36 excluded	Type of surgery: Vascular surgery – aortic or aortoiliac and aneurysmectomy; aorto-femoral bypass for atherosclerotic disease; and femoropopliteal or femorodistal bypass.	Type: LMWH (Enoxaparin) Dose: 2100 IU pre-op, then 4200 IU	Type: Unfractionated heparin Dose: 5000 units pre-op, 7500 units post-op	1 month	DVT Confirmed by: Duplex US, confirmed by venography on 7th-10th day post- op. Earlier if clinical suspicion	Int: 10/122 Control: 4/111 p value: Not significant)	Comments: Numbers in each group for baseline data do not tally with text. Arterial patency also assessed by duplex US scanning. No significant differences observed between groups in terms of development
				Mean duration of surgery: Intervention: 4.2±1.4 h Control:	Timing: Begun day pre-op and repeatedly daily until 7th	Timing: Begun day pre-op and repeated twice daily until 7th day post-op		PE Confirmed by: Clinical suspicion investigated	Int: 0/122 Control: 0/111 p value: N/A	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				4.2±1.5h	day post- op			by angiogram		of post-op arterial thrombosis. Thrombocytopenia (which resolved spontaneously within 3 days) reported in 2 LMWH patients. Not reported: PVT, PTS, QoL, LoS, Funding: Trial supported by grant from Labaratoires Pharmuka, France.
				Intervention: Mean age: 65±11 yrs M/F:101/25	Additional non-comparative prophylaxis: Intraoperative use of UFH (94.4%) or protamine (7.9%) was authorised in both groups	Additional non-comparative prophylaxis: Intraoperative use of UFH (97.4%) or protamine (9.4%) was authorised in both groups		Preoperative red blood cell units	Int: 3.91±2.79 units Control: 3.61±1.91 p value: Not significant	
				Control: Mean age: 64±11 yrs M/F:99/18				Post-operative suction drain volume	Int: 423±438ml Control: 408±455ml p value: Not significant	
				Pre-existing risk factors: Past history of VTE, age, obesity, varicose veins, COPD (no significant diffs between groups apart from COPD – more in LMWH group, p=0.02).				Survival	Int: 120 /122 Control: 111/111 p value: not reported	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Lastoria 2006 [197]	RCT	1+	Total: 75 M/F: 59/16 Int: 41 Cont: 34	Type of surgery: Vascular: Major lower extremity amputation (30 above-knee and 45 below-knee) Inclusion criteria: Patients over 18 years, undergoing elective or emergency lower- limb amputation for critical-limb ischemia. Excluded if had previous venous thrombo-embolism, and patients with contra-indication for anticoagulant prophylaxis.	LMWH (enoxaparin) Dose: 40mg/day Timing: 12 hours before surgery or in emergency cases in the first postoperative day. Duration: During hospitalisation Additional non-comparative prophylaxis: Not reported	UFH Dose: 5000 IU (subcutaneously) Timing: 12 hours before surgery or in emergency cases in the first postoperative day. Duration: During hospitalisation Additional non-comparative prophylaxis: Not reported	NR	DVT confirmed by duplex scanning (5-8 days after surgery)	Int: 4 (9.7%) Cont: 4 (11.7%) P=0.92	Funding: Paulista State University. Not reported: Proximal DVT's, PEs, duration of hospital stay, QoL or post-thrombotic syndrome. Notes: DVT: 1 bilateral thrombosis in each group. No significant difference between interventions in DVTs in level of amputation or sex of patient.
								Major bleeding	Int: 0 Cont: 0	

Study	San Norberto Garcia 2013[285]

Study	San Norberto Garcia 2013[285]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=264)
Countries and setting	Conducted in Spain; Setting:
Line of therapy	1st line
Duration of study	Not clear: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Patients with moderate thromboembolism risk
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	People 18-80 years who were schedule to undergo elective varicose vein surgery
Exclusion criteria	People with low, high or highest risk for VTE; active bleeding; high risk of bleeding; contraindication to bemiparin; condition that might require bemiparin dose adjustment, including severe renal impairment; renal insufficiency; need for anticoagulant therapy; significant liver disease; pregnancy or breastfeeding; concomitant use of HIV protease inhibitors; use of fibrinolytic therapy
Recruitment/selection of patients	Consecutively recruited between 1 January 2010 and 31 March 2010
Age, gender and ethnicity	Age - Mean (range): 67 (18-75). Gender (M:F): 104:162. Ethnicity: Not reported
Further population details	1. Active cancer: No active cancer (No malignancy in either group). 2. BMI : Mixed (obesity (>25kg/m2): LMWH n=66; control n=58). 3. Open versus endovascular: Not stated 4. Renal impairment: Mixed (LMWH n=2; control n=4).
Indirectness of population	No indirectness
Interventions	(n=132) Intervention 1: Low molecular weight heparin (not licensed in UK) - Bemiparin. Bemiparin 2500/3500 IU/day for 10 days at a prophylactic dose plus AES (thigh length) for 3 months, and early ambulation. Bemiparin was started 6 hours after wound closure. Mobilisation consisted of bed to chair at day 1 and ambulation as of day 2. Duration 6 months. Concurrent medication/care: Varicose vein surgery (n=130) Intervention 2: Intermittent pneumatic compression devices - Mixed full leg/below knee. IPCD compression bandages at 20 to 25 mmgHg (Bi-Flex 16; Thuane, France) during first 7 days and then AES at 12-15 mmHg (TED; Codiven, UK). Duration 3 months. Concurrent medication/care: Varicose vein surgery
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEMIPARIN versus COMPRESSION BANDAGES	

Study	San Norberto Garcia 2013[285]
Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: DVT at 3 months; Group 1: 0/132, Group 2: 0/130; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: Symptomatic PE at 3 months; Group 1: 0/130, Group 2: 0/132; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding at up to 45 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: Major bleeding at 3 months; Group 1: 0/130, Group 2: 0/132; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	Wang 2015[330]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2196)
Countries and setting	Conducted in China; Setting: Vascular Surgery Department of The 2nd Affiliated Hospital of Harbin Medical University of China
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Isolated varicose veins of the lower extremity requiring conventional surgery (high ligation and stripping of the great saphenous vein, and removal of superficial varicosities)
Subgroup analysis within study	Stratified then randomised:
Inclusion criteria	Isolated varicose veins of the lower extremity requiring conventional surgery (high ligation and stripping of the great saphenous vein, and removal of superficial varicosities)
Exclusion criteria	prior varicose vein procedure (i.e. surgical stripping, endovenous ablation, sclerotherapy); prior VTE; leg trauma

Study	Wang 2015[330]
	within 2 years; congenital venous malformations (i.e. Klippel–Trenaunay syndrome); autoimmune diseases (i.e. systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome); stenosis or occlusion of the inferior vena cava; anticoagulant, antiplatelet, or hormonal therapy; cancers; or nephrotic syndrome.
Age, gender and ethnicity	Age - Mean (SD): Group A (n=542) 49.95 (10.62); Group B (n=531) 7.84 (11.46); Group C (n=573) 46.86 (11.07); Group D (n=550) 45.92 (9.71). Gender (M:F): Not reported in raw numbers overall. Ethnicity:
Further population details	1. Active cancer: Not stated 2. BMI: Not stated 3. Open versus endovascular: Not stated 4. Renal impairment: Not stated
Indirectness of population	No indirectness
Interventions	(n=542) Intervention 1: No treatment - Usual care. No VTE prophylaxis. Duration 30 days. Concurrent medication/care: Surgery for varicose veins (n=531) Intervention 2: Unfractionated heparin - low dose, administered subcutaneously. Low-dose unfractionated heparin, 125 U/kg per day divided into thrice daily subcutaneous injections . Duration 30 days. Concurrent medication/care: Surgery for varicose veins (n=573) Intervention 3: Low molecular weight heparin (licensed in UK) - Enoxaparin. Enoxaparin sodium 6000 IU once daily. Duration 30 days. Concurrent medication/care: surgery for varicose veins (n=550) Intervention 4: Low molecular weight heparin (licensed in UK) - Enoxaparin. Enoxaparin sodium 4000 IU once daily. Duration 30 days. Concurrent medication/care: surgery for varicose veins
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UFH versus NO VTE PROPHYLAXIS

Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome for People undergoing varicose vein surgery: DVT at 30 days; Group 1: 28/542, Group 2: 3/573; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for People undergoing varicose vein surgery: PE at 30 days; Group 1: 8/542, Group 2: 0/531; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for People undergoing varicose vein surgery: Haemorrhage at 30 days; Group 1: 41/531, Group 2: 1/542; Risk of bias: Low; Indirectness of outcome: Serious indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN 6000 IU versus NO VTE PROPHYLAXIS

Study	Wang 2015[330]
	Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: DVT at 30 days; Group 1: 28/542, Group 2: 2/573; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: PE at 30 days; Group 1: 8/543, Group 2: 0/573; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding at up to 45 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: Haemorrhage at 30 days; Risk of bias: Low; Indirectness of outcome: Serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN 6000 IU versus UFH Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: DVT at 30 days; Group 1: 2/573, Group 2: 3/531; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: PE at 30 days; Group 1: 0/573, Group 2: 0/531; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding at up to 45 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: Haemorrhage at 30 days; Group 1: 1/573, Group 2: 4/531; Risk of bias: Low; Indirectness of outcome: Serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN 6000 IU versus ENOXAPARIN 4000 IU Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: DVT at 30 days; Group 1: 2/573, Group 2: 2/550; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: PE at 30 days; Group 1: 0/573, Group 2: 0/550; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Wang 2015[330]
Protocol outcome 3: Major bleeding at up to 45 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: Haemorrhage at 30 days; Group 1: 1/573, Group 2: 1/550; Risk of bias: Low; Indirectness of outcome: Serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN 4000 IU versus NO VTE PROPHYLAXIS Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: DVT at 30 days; Group 1: 28/542, Group 2: 3/531; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for People undergoing varicose vein surgery: PE at 30 days; Group 1: 8/542, Group 2: 0/550; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Major bleeding at up to 45 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: Haemorrhage at 30 days; Risk of bias: Low; Indirectness of outcome: Serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENOXAPARIN 4000 IU versus UFH Protocol outcome 1: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: DVT at 30 days; Group 1: 2/550, Group 2: 3/531; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Pulmonary embolism at 7-90 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: PE at 30 days; Group 1: 0/550, Group 2: 0/531; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding at up to 45 days from hospital discharge - Actual outcome for People undergoing varicose vein surgery: Haemorrhage at 30 days; Group 1: 0/550, Group 2: 0/531; Risk of bias: Low; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	All-cause mortality at up to 90 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically relevant non-major bleeding at up to 45 days from hospital discharge; Health-related quality of life at up to 90 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge

Study	Ye 2016[346]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=400)
Countries and setting	Conducted in China; Setting: Hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention): 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People undergoing endovenous ablation for primary unilateral great saphenous vein incompetence
Stratum	People undergoing varicose vein surgery:
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 18 and 75 years; primary unilateral great saphenous vein incompetence; C2 clinical type according to the CEAP classification system; no contraindication to surgery.
Exclusion criteria	Previous varicose vein surgery, bilateral treatment during the same procedure, patient refusal to participate in the trial, not suitable for day case surgery, unable to wear elastic stockings, already used elastic stockings or an elastic bandage and patients with arterial disease (ankle brachial index < 0.9).
Recruitment/selection of patients	Enrolled between January 2012 and November 2013
Age, gender and ethnicity	Age - Median (IQR): Compression group 48 (37-59); usual care 49 (40-60). Gender (M:F): 165/235. Ethnicity: NR
Further population details	1. Active cancer: No active cancer 2. BMI : Not obese (BMI under 30 kg/m2) (Mean BMI under 30 kg/m2: compression group 22.5 (3.9), usual care 23.2 (4.1)). 3. Open versus endovascular: Endovascular (endovascular laser ablation). 4. Renal impairment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=200) Intervention 1: Anti-embolism stockings - Above knee. Elastic compression stockings. An elastic bandage was placed on the treated limb after the procedure, while the patient was still on the operating table and left in position during the first night. Patients then wore a thigh-high elastic compression stocking (class II, ankle pressure of 23-32 mmHg) with an open toe distally, during the daytime for at least 2 weeks. Procedure was endovenous laser ablation combined with a high ligation of the great saphenous vein. Duration NR. Concurrent medication/care: Pharmacological prophylaxis for deep vein thrombosis and wound infection were not prescribed. No patients were prescribed analgesics. Patients encouraged to resume their daily activities and return to work as soon as possible. Indirectness: No indirectness

	(n=200) Intervention 2: No treatment - Usual care. Usual care. An elastic bandage was placed on the treated limb after the procedure, while the patient was still on the operating table and left in position during the first night(same as intervention group, then compression stockings were not recommended). Procedure was endovenous laser ablation combined with a high ligation of the great saphenous vein. Duration NR. Concurrent medication/care: Pharmacological prophylaxis for deep vein thrombosis and wound infection were not prescribed. No patients were prescribed analgesics. Patients encouraged to resume their daily activities and return to work as soon as possible. Indirectness: No indirectness
Funding	Academic or government funding (National Natural Science Foundation of CHina, Science and Technology Committee of Shanghai and China Postdoctoral Science Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMPRESSION STOCKINGS (ABOVE KNEE) versus USUAL CARE

Protocol outcome 1: All-cause mortality at up to 90 days from hospital discharge
- Actual outcome for People undergoing varicose vein surgery: Mortality at 2 weeks; Group 1: 0/200, Group 2: 0/200
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 31; Group 2 Number missing: 29

Protocol outcome 2: Deep vein thrombosis (symptomatic and asymptomatic) at 7-90 days from hospital discharge
- Actual outcome for People undergoing varicose vein surgery: DVT found by US duplex at 2 weeks; Group 1: 0/200, Group 2: 0/200
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 31; Group 2 Number missing: 29

Protocol outcome 3: Pulmonary embolism at 7-90 days from hospital discharge
- Actual outcome for People undergoing varicose vein surgery: Symptomatic pulmonary embolism at 2 weeks; Group 1: 0/200, Group 2: 0/200
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 31; Group 2 Number missing: 29

Protocol outcome 4: Health-related quality of life at up to 90 days from hospital discharge
- Actual outcome for People undergoing varicose vein surgery: Aberdeen Varicose Vein Symptoms Severity Score (AVVSS) at 4 weeks; Group 1: mean 8.5 (SD 3.6); n=200, Group 2: mean 8 (SD 3.4); n=200
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 31; Group 2 Number missing: 29

Protocol outcomes not reported by the study	Major bleeding at up to 45 days from hospital discharge; Fatal PE at up to 90 days from hospital discharge; Clinically

	relevant non-major bleeding at up to 45 days from hospital discharge; Heparin-induced thrombocytopenia at up to 90 days from hospital discharge; Technical complications of mechanical interventions at up to 90 days from hospital discharge;

H.37 Head and neck surgery

H.37.1 Oral and maxillofacial surgery

No relevant clinical studies were identified.

H.37.2 Ear, nose and throat (ENT) surgery

No relevant clinical studies were identified.

Appendix I: References

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