National Institute for Health and Care Excellence

Venous thromboembolism in over 16s

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

NICE guideline NG89 (volume 1)

Methods, evidence and recommendations

March 2018

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Update information

January 2021: Recommendations on assessing patients on admission to hospital to identify the risk of VTE and bleeding were amended to clarify that the Department of Health tool is commonly used to develop a treatment plan.

November 2020: We added links in the sections on acutely ill medical patients and interventions for critical care to the NICE COVID-19 rapid guideline on reducing the risk of venous thromboembolism in over 16s.

December 2019: The recommendation on British Standards for anti-embolism hosiery were updated because BS 6612 and BS 7672 have been withdrawn.

August 2019: Recommendation 1.12.11 (1.5.30 in this document) was amended to clarify when anti-embolism stockings can be used for VTE prophylaxis for people with spinal injury.

For the current recommendations, see:
www.nice.org.uk/guidance/NG89/chapter/recommendations

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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.

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1 Guideline summary

1.1 Full list of recommendations

Risk assessment

1.1.1 Assess all patients to identify the risk of venous thromboembolism (VTE) and bleeding (see recommendations 1.1.2, 1.1.5, 1.1.9, 1.4.17 and 1.4.23).

People admitted to hospital

Medical patients

1.1.2 Assess all medical patients to identify the risk of VTE and bleeding:

- as soon as possible after admission to hospital or by the time of the first consultant review

- using a tool published by a national UK body, professional network or peer-reviewed journal. The most commonly used risk assessment tool for medical patients is the Department of Health VTE risk assessment tool[a] (see Appendix T). [**2018**]

1.1.3 Balance the person's individual risk of VTE against their risk of bleeding when deciding whether to offer pharmacological thromboprophylaxis to medical patients. **[2018]**

1.1.4 If using pharmacological VTE prophylaxis for medical patients, start it as soon as possible and within 14 hours of admission, unless otherwise stated in the population-specific recommendations (see chapters 9-13). **[2018]**

Surgical and trauma patients

1.1.5 Assess all surgical and trauma patients to identify the risk of VTE and bleeding:

- as soon as possible after admission to hospital or by the time of the first consultant review

- using a tool published by a national UK body, professional network or peer-reviewed journal. The most commonly used risk assessment tool for surgical patients is the Department of Health VTE risk assessment tool[b] (See Appendix T). **[2018]**

1.1.6 Balance the person's individual risk of VTE against their risk of bleeding when deciding whether to offer pharmacological thromboprophylaxis to surgical and trauma patients. **[2018]**

1.1.7 If using pharmacological VTE prophylaxis for surgical and trauma patients, start it as soon as possible and within 14 hours of admission, unless otherwise stated in the population-specific recommendations (see chapters 9-13). **[2018]**

Reassessment of risk of VTE and bleeding

1.1.8 Reassess all medical, surgical and trauma patients for risk of VTE and bleeding at the point of consultant review or if their clinical condition changes. **[2018]**

Pregnant women and women who gave birth or had a miscarriage or termination of pregnancy in the past 6 weeks

1.1.9 Assess all women on admission to hospital or midwife-led unit if they are pregnant or gave birth, had a miscarriage or had a termination of pregnancy in the past 6 weeks, to identify their

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b Reproduced with the permission of the Department of Health and Social Care under the Open Government Licence.

risk of VTE and bleeding. Use a tool published by a national UK body, professional network or peer-reviewed journal. The most commonly used risk assessment tool was developed by the Royal College of Obstetricians and Gynaecologists[c] (See Appendix U). **[2018]**

1.1.10 Reassess risk of VTE and bleeding, and assess the need for thromboprophylaxis for all women:

- within 6 hours of giving birth, having a miscarriage or having a termination of pregnancy **or**

- if their clinical condition changes **and** they:
    - are pregnant **or**
    - gave birth, had a miscarriage or had a termination of pregnancy within the past 6 weeks. **[2018]**

1.2 Giving information and planning for discharge

1.2.1 On admission ensure that people understand the reason for having a risk assessment for VTE and bleeding. **[2018]**

1.2.2 For people admitted to hospital who are at increased risk of VTE, give them and their family members or carers (as appropriate) verbal and written information on the following before offering VTE prophylaxis:

- the person's risks and possible consequences of VTE

- the importance of VTE prophylaxis and its possible side effects – for example, pharmacological prophylaxis can increase bleeding risk

- the correct use of VTE prophylaxis – for example, anti-embolism stockings, intermittent pneumatic compression

- how people can reduce their risk of VTE (such as keeping well hydrated and, if possible, exercising and becoming more mobile). **[2018]**

1.2.3 Be aware that heparins are of animal origin and this may be of concern to some people[d]. Discuss the alternatives with people who have concerns about using animal products, after discussing their suitability, advantages and disadvantages with the person. **[2018]**

1.2.4 As part of the discharge plan, give patients and their family members or carers (as appropriate) verbal and written information on:

- the signs and symptoms of deep vein thrombosis (DVT) and pulmonary embolism (PE)

- how people can reduce their risk of VTE (such as keeping well hydrated and, if possible, exercising and becoming more mobile)

- the importance of seeking help if DVT, PE or other adverse events are suspected. **[2018]**

1.2.5 Give people discharged with VTE prophylaxis and their family members or carers (as appropriate) verbal and written information on:

- the importance of using VTE prophylaxis correctly (including the correct administration and disposal of pharmacological prophylaxis)

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c Reproduced from: Royal College of Obstetricians and Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG, 2015, with the permission of the Royal College of Obstetricans and Gynaecologists.

d See Religion or belief: a practical guide for the NHS.

- the importance of continuing treatment for the recommended duration

- the signs and symptoms of adverse events related to VTE prophylaxis

- the importance of seeking help and who to contact if people have problems using VTE prophylaxis. **[2018]**

1.2.6 Ensure that people who are discharged with anti-embolism stockings:

- understand the benefits of wearing them

- understand the importance of wearing them correctly

- understand the need to remove them daily for hygiene purposes

- are able to remove and replace them, or have someone available who will be able to do this for them

- know what to look for if there is a problem – for example, skin marking, blistering or discolouration, particularly over the heels and bony prominences

- know who to contact if there is a problem

- know when to stop wearing them. **[2018]**

1.2.7 Ensure that people who are discharged with pharmacological and/or mechanical VTE prophylaxis are able to use it correctly, or have arrangements made for someone to be available who will be able to help them. **[2018]**

1.2.8 Notify the person's GP if the person has been discharged with pharmacological and/or mechanical VTE prophylaxis to be used at home. **[2018]**

1.3 All patients

Mechanical prophylaxis

1.3.1 Do not offer anti-embolism stockings to people who have:

- suspected or proven peripheral arterial disease

- peripheral arterial bypass grafting

- peripheral neuropathy or other causes of sensory impairment

- any local conditions in which anti-embolism stockings may cause damage – for example, fragile 'tissue paper' skin, dermatitis, gangrene or recent skin graft

- known allergy to material of manufacture

- severe leg oedema

- major limb deformity or unusual leg size or shape preventing correct fit.

   Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds. **[2010, amended 2018]**

1.3.2 Ensure that people who need anti-embolism stockings have their legs measured and that they are provided with the correct size of stocking. Anti-embolism stockings should be fitted and patients shown how to use them by staff trained in their use. **[2010]**

1.3.3 Ensure that people who develop oedema or postoperative swelling have their legs re-measured and anti-embolism stockings refitted. **[2010]**

1.3.4 If arterial disease is suspected, seek expert opinion before fitting anti-embolism stockings. **[2010]**

1.3.5 Use anti-embolism stockings that provide graduated compression and produce a calf pressure of 14–15 mmHg. (This relates to a pressure of 14–18 mmHg at the ankle and is in line with British Standards 6612:1985 Specification for graduated compression hosiery and 7672:1993 Specification for compression, stiffness and labelling of anti-embolism hosiery.) **[2010]**

1.3.6 Encourage people to wear their anti-embolism stockings day and night until they no longer have significantly reduced mobility. **[2010]**

1.3.7 Remove anti-embolism stockings daily for hygiene purposes and to inspect skin condition. In people with a significant reduction in mobility, poor skin integrity or any sensory loss, inspect the skin 2 or 3 times a day, particularly over the heels and bony prominences. **[2010]**

1.3.8 Monitor the use of anti-embolism stockings and offer assistance if they are not being worn correctly. **[2010]**

1.3.9 Stop the use of anti-embolism stockings if there is marking, blistering or discolouration of the skin, particularly over the heels and bony prominences, or if the person experiences pain or discomfort. If suitable, offer intermittent pneumatic compression as an alternative. **[2010, amended 2018]**

1.3.10 Do not offer intermittent pneumatic compression to people with a known allergy to the material of manufacture. **[2010, amended 2018]**

1.3.11 Advise the person to wear their device for as much time as possible. **[2010, amended 2018]**

Pharmacological prophylaxis

1.3.12 For pharmacological VTE prophylaxis in people under 18 follow the recommendations on apixaban, aspirin, dabigatran etexilate, fondaparinux sodium, LMWH and rivaroxaban in this guideline. At the time of publication (March 2018) these drugs did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. **[2018]**

All surgery

1.3.13 Advise people to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods. **[2010]**

Nursing care: early mobilisation and hydration

1.3.14 Encourage people to mobilise as soon as possible. **[2010]**

1.3.15 Do not allow people to become dehydrated unless clinically indicated. **[2010]**

People using antiplatelet agents

1.3.16 Consider VTE prophylaxis for people who are having antiplatelet agents for other conditions and whose risk of VTE outweighs their risk of bleeding. Take into account the risk of bleeding and of comorbidities such as arterial thrombosis.

- If the risk of VTE outweighs the risk of bleeding, consider pharmacological VTE prophylaxis based on their condition or procedure.

- If the risk of bleeding outweighs the risk of VTE, consider mechanical VTE prophylaxis. **[2018]**

People using anticoagulation therapy

1.3.17   Consider VTE prophylaxis for people at increased risk of VTE who are interrupting anticoagulant therapy. [2018]

1.4 Medical patients

Acute coronary syndromes

1.4.1   Be aware that people receiving anticoagulant drugs as part of their treatment for an acute coronary syndrome do not usually need VTE prophylaxis. See also recommendation 1.3.17. **[2018]**

Acute stroke patients

1.4.2   Do not offer anti-embolism stockings for VTE prophylaxis to people who are admitted for acute stroke. **[2010, amended 2018]**

1.4.3   Consider intermittent pneumatic compression for VTE prophylaxis for people who are immobile and admitted with acute stroke. If using, start it within 3 days of acute stroke. **[2018]**

1.4.4   Explain to the person admitted with acute stroke and their family members or carers (as appropriate) that intermittent pneumatic compression:

- reduces the risk of deep vein thrombosis and may increase their chances of survival

- will not help them recover from stroke, and there may be an associated increased risk of surviving with severe disability. **[2018]**

1.4.5   When using intermittent pneumatic compression for people who are admitted with acute stroke, provide it for 30 days or until the person is mobile or discharged, whichever is sooner. **[2018]**

Acutely ill medical patients

1.4.6   Offer pharmacological VTE prophylaxis for a minimum of 7 days to acutely ill medical patients whose risk of VTE outweighs their risk of bleeding:

- Use low-molecular-weight heparin (LMWH)[e] as first-line treatment.

If LMWH[f] is contraindicated use fondaparinux sodium[g]. **[2018]**

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[e] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[f] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[g] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full

People with renal impairment

1.4.7   If using pharmacological VTE prophylaxis for people with renal impairment choose either LMWH[h] or unfractionated heparin (UFH). **[2018]**

1.4.8   If needed, reduce the dose of LMWH[i] and UFH for people with renal impairment. Base the decision on multidisciplinary or senior opinion, or locally agreed protocols. **[2018]**

People with cancer

1.4.9   Do not offer VTE prophylaxis to people with cancer who are receiving cancer modifiying treatments such as radiotherapy, chemotherapy or immunotherapy and who are mobile, except as outlined in recommendations 1.4.10 and 1.4.11, unless they are also at increased risk of VTE because of something other than the cancer. **[2018]**

1.4.10   Consider pharmacological VTE prophylaxis for people with myeloma who are receiving chemotherapy with thalidomide, pomalidomide or lenalidamide with steroids. Choose either:

- aspirin[j] (75 or 150 mg) **or**

- LMWH[k]. **[2018]**

1.4.11   Consider pharmacological VTE prophylaxis with LMWH[l] for people with pancreatic cancer who are receiving chemotherapy. **[2018]**

1.4.12 If giving VTE prophylaxis to people with cancer (see recommendations 1.4.10 and 1.4.11) continue for as long as they are receiving chemotherapy. **[2018]**

Palliative care

1.4.13   Consider pharmacological VTE prophylaxis for people who are having palliative care. Take into account temporary increases in thrombotic risk factors, risk of bleeding, likely life expectancy and the views of the person and their family members or carers (as appropriate):

- Use LMWH[m] as first-line treatment.

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responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[h] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[i] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[j]   At the time of publication (March 2018), aspirin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[k] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[l] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[m] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the

- If LMWH[n] is contraindicated use fondaparinux sodium[o]. **[2018]**

1.4.14 Do not offer VTE prophylaxis to people in the last days of life. **[2018]**

1.4.15 For recommendations on shared decision-making in the last days of life, see the NICE guideline on care of dying adults in the last days of life. **[2018]**

1.4.16 Review VTE prophylaxis daily for people who are having palliative care, taking into account the views of the person, their family members or carers (as appropriate) and the multidisciplinary team. **[2018]**

People admitted to critical care

1.4.17 Assess all people admitted to the critical care unit for risk of VTE and bleeding. **[2018]**

1.4.18 Provide LMWH[p] to people admitted to the critical care unit if pharmacological VTE prophylaxis is not contraindicated. For people with renal impairment see recommendations 1.4.7 and 1.4.8. **[2018]**

1.4.19 Consider mechanical VTE prophylaxis for people admitted to the critical care unit if pharmacological prophylaxis is contraindicated based on their condition or procedure. **[2018]**

1.4.20 If using mechanical VTE prophylaxis for people admitted to the critical care unit, start it on admission and continue until the person no longer has reduced mobility relative to their normal or anticipated mobility. **[2018]**

1.4.21 Reassess VTE and bleeding risk daily for people in critical care units. **[2018]**

1.4.22 Assess VTE and bleeding risk more than once a day in people admitted to the critical care unit if the person's condition is changing rapidly. **[2018]**

People with psychiatric illness

1.4.23 Assess all acute psychiatric patients to identify their risk of VTE and bleeding:

- as soon as possible after admission to hospital or by the time of the first consultant review

- using a tool published by a national UK body, professional network or peer-reviewed journal. The most commonly used risk assessment tool for hospital patients is the Department of Health VTE risk assessment tool[q] (See Appendix T). **[2018]**

1.4.24 Reassess all people admitted to an acute psychiatric ward for risk of VTE and bleeding at the point of consultant review or if their clinical condition changes. **[2018]**

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decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[n] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[o] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[p] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

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1.4.25   Consider pharmacological VTE prophylaxis with LMWH[r] for people admitted to an acute psychiatric ward whose risk of VTE outweighs their risk of bleeding. **[2018]**

1.4.26   Consider pharmacological VTE prophylaxis with fondaparinux sodium[s] if LMWH[t] is contraindicated for people admitted to an acute psychiatric ward whose risk of VTE outweighs their risk of bleeding. **[2018]**

1.4.27   Continue pharmacological VTE prophylaxis for people admitted to an acute psychiatric ward until the person is no longer at increased risk of VTE. **[2018]**

1.5 Surgical and trauma patients

Anaesthesia

1.5.1   Consider regional anaesthesia for individual patients, in addition to other methods of VTE prophylaxis, as it carries a lower risk of VTE than general anaesthesia. Take into account the person's preferences, their suitability for regional anaesthesia and any other planned method of VTE prophylaxis. **[2010]**

1.5.2   If regional anaesthesia is used, plan the timing of pharmacological VTE prophylaxis to minimise the risk of epidural haematoma. If antiplatelet or anticoagulant agents are being used, or their use is planned, refer to the summary of product characteristics for guidance about the safety and timing of these in relation to the use of regional anaesthesia. **[2010]**

1.5.3   Do not routinely offer pharmacological or mechanical VTE prophylaxis to people undergoing a surgical procedure with local anaesthesia by local infiltration with no limitation of mobility. **[2010]**

Lower limb immobilisation

1.5.4   Consider pharmacological VTE prophylaxis with LMWH[u] or fondaparinux sodium[v] for people with lower limb immobilisation whose risk of VTE outweighs their risk of bleeding. Consider stopping prophylaxis if lower limb immobilisation continues beyond 42 days. **[2018]**

Fragility fractures of the pelvis, hip and proximal femur

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[r] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[s] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[t] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[u] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[v] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

1.5.5 Offer VTE prophylaxis for a month to people with fragility fractures of the pelvis, hip or proximal femur if the risk of VTE outweighs the risk of bleeding Choose either:

- LMWH[w], starting 6–12 hours after surgery **or**

- fondaparinux sodium[x], starting 6 hours after surgery, providing there is low risk of bleeding. **[2018]**

1.5.6 Consider pre-operative VTE prophylaxis for people with fragility fractures of the pelvis, hip or proximal femur if surgery is delayed beyond the day after admission. Give the last dose no less than 12 hours before surgery for LMWH[y] or 24 hours before surgery for fondaparinux sodium[z]. **[2018]**

1.5.7 Consider intermittent pneumatic compression for people with fragility fractures of the pelvis, hip or proximal femur at the time of admission if pharmacological prophylaxis is contraindicated. Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

Elective hip replacement

1.5.8 Offer VTE prophylaxis to people undergoing elective hip replacement surgery whose risk of VTE outweighs their risk of bleeding. Choose any one of:

- LMWH[aa] for 10 days followed by aspirin[bb] (75 or 150 mg) for a further 28 days.

- LMWH[cc] for 28 days combined with anti-embolism stockings (until discharge).

- Rivaroxaban[dd]. Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip

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[w] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[x] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[y] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[z] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

[aa] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[bb] At the time of publication (March 2018), aspirin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[cc] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[dd] At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for

replacement surgery or elective total knee replacement surgery. [This text is from Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (NICE technology appraisal guidance 170).] **[2018]**

1.5.9   Consider one of the following if none of the options in recommendation 1.5.8 can be used:

- Apixaban[ee] is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. [This text is from Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (NICE technology appraisal guidance 245).]

- Dabigatran etexilate[ff], within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (NICE technology appraisal guidance 157).]

1.5.10   Consider anti-embolism stockings until discharge from hospital if pharmacological interventions are contraindicated in people undergoing elective hip replacement surgery. **[2018]**

Elective knee replacement

1.5.11   Offer VTE prophylaxis to people undergoing elective knee replacement surgery whose VTE risk outweighs their risk of bleeding. Choose any one of:

- Aspirin[gg] (75 or 150 mg) for 14 days.

- LMWH[hh] for 14 days combined with anti-embolism stockings until discharge.

- Rivaroxaban[ii]. Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (NICE technology appraisal guidance 170).] [2018]

1.5.12   Consider one of the following if none of the options in recommendation 1.5.11 can be used:

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the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

ee   At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

ff   At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

gg   At the time of publication (March 2018), aspirin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

hh   At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

ii   At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- Apixaban[jj] is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. [This text is from Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (NICE technology appraisal guidance 245).]

- Dabigatran etexilate[kk], within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (NICE technology appraisal guidance 157).]

1.5.13   Consider intermittent pneumatic compression if pharmacological prophylaxis is contraindicated in people undergoing elective knee replacement surgery. Continue until the person is mobile. **[2018]**

Non-arthroplasty orthopaedic knee surgery

1.5.14   Be aware that VTE prophylaxis is generally not needed for people undergoing arthroscopic knee surgery where:

- total anaesthesia time is less than 90 minutes **and**

- the person is at low risk of VTE. **[2018]**

1.5.15   Consider LMWH[ll] 6–12 hours after surgery for 14 days for people undergoing arthroscopic knee surgery if:

- total anaesthesia time is more than 90 minutes **or**

- the person's risk of VTE outweighs their risk of bleeding. **[2018]**

1.5.16   Consider VTE prophylaxis for people undergoing other knee surgery (for example, osteotomy or fracture surgery) whose risk of VTE outweighs their risk of bleeding. **[2018]**

Foot and ankle orthopaedic surgery

1.5.17   Consider pharmacological VTE prophylaxis for people undergoing foot or ankle surgery:

- that requires immobilisation (for example, arthrodesis or arthroplasty). Consider stopping prophylaxis if immobilisation continues beyond 42 days (see recommendation 1.5.4) **or**

- when total anaesthesia time is more than 90 minutes **or**

- the person's risk of VTE outweighs their risk of bleeding. **[2018]**

Upper limb orthopaedic surgery

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jj   At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

kk   At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

ll   At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

1.5.18   Be aware that VTE prophylaxis is generally not needed if giving local or regional anaesthetic for upper limb surgery. **[2018]**

1.5.19   Consider VTE prophylaxis for people undergoing upper limb surgery if the person's total time under general anaesthetic is over 90 minutes or where their operation is likely to make it difficult for them to mobilise. **[2018]**

Elective spinal surgery

1.5.20   Offer mechanical VTE prophylaxis on admission to people undergoing elective spinal surgery. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression.

   Continue for 30 days or until the person is mobile or discharged, whichever is sooner. **[2018]**

1.5.21   Consider adding pharmacological VTE prophylaxis with LMWH^mm for people undergoing elective spinal surgery whose risk of VTE outweighs their risk of bleeding, taking into account individual patient and surgical factors (major or complex surgery) and according to clinical judgement. **[2018]**

1.5.22   If using LMWH^nn for people undergoing elective spinal surgery, start giving it 24–48 hours postoperatively according to clinical judgement, taking into account patient characteristics and surgical procedure. Continue for 30 days or until the person is mobile or discharged, whichever is sooner. **[2018]**

1.5.23   If needed, start LMWH^oo earlier than 24 hours after the operation for people undergoing elective spinal surgery. Base the decision on multidisciplinary or senior opinion, or a locally agreed protocol. **[2018]**

Cranial surgery

1.5.24   Consider mechanical VTE prophylaxis for people undergoing cranial surgery. **[2018]**

1.5.25   If using mechanical VTE prophylaxis for people undergoing cranial surgery, start it on admission. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression.

   Continue for 30 days or until the person is mobile or discharged, whichever is sooner. **[2018]**

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mm At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

nn At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

oo At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

1.5.26   Consider adding pre-operative pharmacological VTE prophylaxis with LMWH[pp]. Give the last dose no less than 24 hours before surgery for people undergoing cranial surgery whose risk of VTE outweighs their risk of bleeding. **[2018]**

1.5.27   Consider adding pharmacological VTE prophylaxis with LMWH[qq], starting 24–48 hours after surgery for people undergoing cranial surgery whose risk of VTE outweighs their risk of bleeding. Continue for a minimum of 7 days. **[2018]**

1.5.28   If needed, start LMWH[rr] earlier than 24 hours after the operation for people undergoing cranial surgery. Base the decision on multidisciplinary or senior opinion, or a locally agreed protocol. **[2018]**

1.5.29   Do not offer pharmacological VTE prophylaxis to people with ruptured cranial vascular malformations (for example, brain aneurysms) or people with intracranial haemorrhage (spontaneous or traumatic) until the lesion has been secured or the condition has stabilised. **[2018]**

Spinal injury

1.5.30   Consider mechanical VTE prophylaxis on admission for people with spinal injury. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression. **[2018]**

1.5.31   Reassess risk of bleeding 24 hours after initial admission in people with spinal injury. **[2018]**

1.5.32   Consider adding pharmacological VTE prophylaxis with LMWH[ss] 24 hours after initial admission for people with spinal injury who are not having surgery in the next 24–48 hours, if the benefit of reducing the risk of VTE outweighs the risk of bleeding. **[2018]**

1.5.33   Continue VTE prophylaxis in people with spinal injury for 30 days or until the person is mobile or discharged, whichever is sooner. **[2018]**

Major trauma

1.5.34   Offer mechanical VTE prophylaxis with intermittent pneumatic compression on admission to people with serious or major trauma. Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

1.5.35   Reassess risk of VTE and bleeding in people with serious or major trauma whenever their clinical condition changes and at least daily. **[2018]**

[pp] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[qq] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[rr] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[ss] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

1.5.36   Consider pharmacological VTE prophylaxis for people with serious or major trauma as soon as possible after the risk assessment when the risk of VTE outweighs the risk of bleeding. Continue for a minimum of 7 days. **[2018]**

Abdominal surgery

1.5.37   Offer VTE prophylaxis to people undergoing abdominal (gastrointestinal, gynaecological, urological) surgery who are at increased risk of VTE. For people undergoing bariatric surgery, follow recommendations 1.5.41–1.5.43. **[2018]**

1.5.38   Start mechanical VTE prophylaxis on admission for people undergoing abdominal surgery. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression.

    Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

1.5.39   Add pharmacological VTE prophylaxis for a minimum of 7 days for people undergoing abdominal surgery whose risk of VTE outweighs their risk of bleeding, taking into account individual patient factors and according to clinical judgement. Choose either:

- LMWH[tt] **or**

- fondaparinux sodium[uu]. **[2018]**

1.5.40   Consider extending pharmacological VTE prophylaxis to 28 days postoperatively for people who have had major cancer surgery in the abdomen. **[2018]**

Bariatric surgery

1.5.41   Offer VTE prophylaxis to people undergoing bariatric surgery. **[2018]**

1.5.42   Start mechanical VTE prophylaxis on admission for people undergoing bariatric surgery. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression.

    Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

1.5.43   Add pharmacological VTE prophylaxis for people undergoing bariatric surgery for a minimum of 7 days for people whose risk of VTE outweighs their risk of bleeding. Choose either:

[tt] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[uu] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- LMWH^{vv} **or**

- fondaparinux sodium^{ww}. **[2018]**

Cardiac surgery

1.5.44   Consider mechanical VTE prophylaxis on admission for people who are undergoing cardiac surgery who are at increased risk of VTE. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression.

Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

1.5.45   Consider adding pharmacological VTE prophylaxis for a minimum of 7 days for people who are undergoing cardiac surgery and are not having other anticoagulation therapy:

- Use LMWH^{xx} as first-line treatment.

- If LMWH^{yy} is contraindicated use fondaparinux sodium^{zz}. **[2018]**

Thoracic surgery

1.5.46   Consider VTE prophylaxis for people undergoing thoracic surgery who are at increased risk of VTE. **[2018]**

1.5.47   Start mechanical VTE prophylaxis on admission for people undergoing thoracic surgery. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression.

Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

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^{vv} At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

^{ww} At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

^{xx} At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

^{yy} At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

^{zz} At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

1.5.48   Consider adding pharmacological VTE prophylaxis for people undergoing thoracic surgery for a minimum of 7 days to people whose risk of VTE outweighs their risk of bleeding:

- Use LMWH[aaa] as first-line treatment.

- If LMWH[bbb] is contraindicated use fondaparinux sodium[ccc]. **[2018]**

Vascular surgery

Open vascular surgery or endovascular aneurysm repair

1.5.49   Consider pharmacological VTE prophylaxis with LMWH[ddd] for a minimum of 7 days for people who are undergoing open vascular surgery or major endovascular procedures, including endovascular aneurysm repair whose risk of VTE outweighs their risk of bleeding. **[2018]**

1.5.50   Consider mechanical VTE prophylaxis on admission for people who are undergoing open vascular surgery or major endovascular procedures, including endovascular aneurysm repair, if pharmacological prophylaxis is contraindicated. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression.

   Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

Lower limb amputation

1.5.51   Consider pharmacological VTE prophylaxis with LMWH[eee] for a minimum of 7 days for people who are undergoing lower limb amputation whose risk of VTE outweighs their risk of bleeding. **[2018]**

1.5.52   Consider mechanical VTE prophylaxis with intermittent pneumatic compression on the contralateral leg, on admission, for people who are undergoing lower limb amputation and if pharmacological prophylaxis is contraindicated. **[2018]**

1.5.53   For people undergoing lower limb amputation, continue mechanical VTE prophylaxis until the person no longer has significantly reduced mobility relative to their anticipated mobility. **[2018]**

[aaa] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[bbb] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[ccc] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[ddd] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[eee] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Varicose vein surgery

1.5.54   Be aware that VTE prophylaxis is generally not needed for people undergoing varicose vein surgery where:

- total anaesthesia time is less than 90 minutes **and**

- the person is at low risk of VTE. **[2018]**

1.5.55   Consider pharmacological VTE prophylaxis with LMWH[fff], starting 6–12 hours after surgery and continuing for 7 days for people undergoing varicose vein surgery if:

- total anaesthesia time is more than 90 minutes **or**

- the person's risk of VTE outweighs their risk of bleeding. **[2018]**

1.5.56   Consider mechanical VTE prophylaxis with anti-embolism stockings, on admission, for people undergoing varicose vein surgery:

- who are at increased risk of VTE **and**

- if pharmacological prophylaxis is contraindicated. **[2018]**

1.5.57   If using anti-embolism stockings for people undergoing varicose vein surgery, continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

Head and neck surgery

Oral and maxillofacial surgery

1.5.58   Consider pharmacological VTE prophylaxis with LMWH[ggg] for a minimum of 7 days for people undergoing oral or maxillofacial surgery whose risk of VTE outweighs their risk of bleeding. **[2018]**

1.5.59   Consider mechanical VTE prophylaxis on admission for people undergoing oral or maxillofacial surgery who are at increased risk of VTE and high risk of bleeding. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression.

    Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

ENT surgery

1.5.60   Consider pharmacological VTE prophylaxis with LMWH[hhh] for a minimum of 7 days for people undergoing ears, nose and throat (ENT) surgery whose risk of VTE outweighs their risk of bleeding. **[2018]**

[fff] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[ggg] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

1.5.61 Consider mechanical VTE prophylaxis on admission for people undergoing ENT surgery who are at increased risk of VTE and high risk of bleeding. Choose either:

- anti-embolism stockings **or**

- intermittent pneumatic compression.

    Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

1.6 Pregnant women and women who gave birth or had a miscarriage or termination of pregnancy in the past 6 weeks

1.6.1 Consider LMWH[iii] for all women who are admitted to hospital or a midwife-led unit if they are pregnant or gave birth, had a miscarriage or had a termination of pregnancy in the past 6 weeks, and whose risk of VTE outweighs their risk of bleeding. **[2018]**

1.6.2 Do not offer VTE prophylaxis to women admitted to hospital or a midwife-led unit who are in active labour. **[2018]**

1.6.3 Stop pharmacological VTE prophylaxis when women are in labour. **[2018]**

1.6.4 If using LMWH[jjj] in pregnant women, start it as soon as possible and within 14 hours of the risk assessment being completed and continue until the woman is no longer at increased risk of VTE or until discharge from hospital or the midwife-led unit. **[2018]**

1.6.5 If using LMWH[kkk] in women who gave birth or had a miscarriage or termination of pregnancy, start 4–8 hours after the event unless contraindicated and continue for a minimum of 7 days. **[2018]**

1.6.6 Consider combined prophylaxis with LMWH[lll] plus mechanical prophylaxis for pregnant women or women who gave birth or had a miscarriage or termination of pregnancy in the past 6 weeks and who are likely to be immobilised, or have significantly reduced mobility relative to their normal or anticipated mobility for 3 or more days after surgery, including caesarean section:

- Use intermittent pneumatic compression as first-line treatment.

- If intermittent pneumatic compression is contraindicated use antiembolism stockings.

[hhh] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[iii] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[jjj] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[kkk] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[lll] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Continue until the woman no longer has significantly reduced mobility relative to her normal or anticipated mobility or until discharge from hospital. **[2018]**

1.2 Key research recommendations

- What is the accuracy of individual risk assessment tools in predicting the risk of VTE and risk of bleeding in people admitted to hospital?

- What is the clinical and cost effectiveness of weight-based dose-adjustment strategies of LMWH compared with fixed dose strategies of LMWH for preventing VTE in people who are very obese (BMI >35) who are admitted to hospital or having day procedures (including surgery and chemotherapy)?

- What is the clinical and cost effectiveness of direct oral anticoagulants (DOACs) for preventing VTE in people with lower limb immobilisation?

- What is the clinical and cost effectiveness of aspirin alone versus other pharmacological and/or mechanical prophylaxis strategies (alone or in combination) for people with fragility fractures of the pelvis, hip or proximal femur?

- What is the clinical and cost effectiveness of standard versus extended duration pharmacological prophylaxis for preventing VTE in people undergoing elective total hip replacement surgery?

1.3 How this guideline was updated

The majority of the previous guideline was updated. Content from 2010 CG92 Venous thromboembolism guideline that has not been updated and retained in this guideline has been marked with grey highlighting throughout. Rationale for changes to recommendations can be found in the relevant linking evidence to recommendations sections and in the table in appendix S.

2 Introduction

Hospital-acquired venous thromboembolism (VTE), also known as hospital-acquired or hospital-associated thrombosis (HAT), covers all VTE that occurs in hospital and within 90 days after a hospital admission. It is a common and potentially preventable problem. VTE most frequently occurs in the deep veins of the legs or pelvis (a deep vein thrombosis). If it dislodges and travels to the lungs it is called a pulmonary embolism, which in some cases can be fatal.

Hospital-acquired VTE accounts for thousands of deaths annually in the NHS, and fatal pulmonary embolism remains a common cause of in-hospital mortality. HAT accounts for 50–60% of all VTE seen. In 2013–14 there were around 24,700 admissions for pulmonary embolism and 19,400 for DVT in England. In 2013, in England and Wales there were 2,191 deaths recorded as due to pulmonary embolism and 2,816 due to deep vein thrombosis. Treatment of non-fatal symptomatic VTE and related long-term morbidities is associated with a considerable cost to the health service.

People admitted to hospital have varying risk factors for VTE. The spectrum of VTE risk is broad, and understanding the scale of the problem has led to a paradigm shift in preventing and managing VTE in the NHS. In particular, patients now undergo VTE risk assessment as a routine event in all NHS care pathways. By July 2013, 96% of adult admissions to NHS-funded acute care hospitals were risk assessed compared with less than 50% of patients in July 2010.

VTE prophylaxis has been shown to reduce the incidence of DVT. It includes mechanical methods (such as anti-embolism stockings, foot impulse and intermittent pneumatic compression devices) and pharmacological treatments (such as heparin and other anticoagulant drugs).

This guideline is about reducing the risk of VTE in people over 16 years of age admitted to hospitals. It provides recommendations on the most clinically and cost effective measures to reduce the risk of VTE, while considering the potential risks of the various VTE prophylaxis options and patient preferences. It highlights the importance of risk assessment for VTE and for bleeding for all people being admitted and of clinical judgement in deciding on a prophylaxis strategy for each person at risk.

The 2018 update takes into account newer evidence and newer therapies and has been made more relevant for specific groups such as surgical sub-specialities, people with mental health conditions and pregnant women.

3 Development of the guideline

3.1 What is a NICE guideline?

NICE guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. These may also include elements of social care or public health measures. We base our guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- A guideline topic is referred to NICE from NHS England.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Guideline Centre (NGC).
- The NGC establishes a guideline committee.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NGC and NICE produce a number of versions of this guideline:

- The 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence.
- The 'short guideline' lists the recommendations.
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

3.2 Remit

NICE received the remit for this guideline from NHS England. NICE commissioned the NGC to produce the guideline.

The remit for this guideline is:

'Venous thromboembolism in over 16s – reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism (update)'

3.3 Who developed this guideline?

A multidisciplinary guideline committee comprising health professionals and researchers as well as lay members developed this guideline (see the list of committee members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Guideline Centre (NGC) and thus supported the development of this guideline. The committee was convened by the NGC and chaired by Professor Gerry Stansby from September 2015 up to February 2017, Dr Peter Barry from April 2017 for the rest of the guideline development. Gerry Stansby stepped down as chair because two systematic reviews were published with him as a contributing author during the guideline development. NICE's conflict of interest policy states that Chairs of advisory committees are in a special position in relation to the work of their committee and so may not have any specific financial or non-financial personal, non-personal or family interests.

The group met approximately every 4 weeks during the development of the guideline. At the start of the guideline development process all committee members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in appendix B.

Two subgroups were convened separate to the committee to provide specific expert guidance on VTE prophylaxis for orthopaedic and obstetric patients.
1. The orthopaedic subgroup was chaired by Professor Gerry Stansby and comprised the orthopaedic surgeon from the main committee, a lay member from the main committee and 4 co-opted orthopaedic consultants representing a range of orthopaedic specialties. The group met 6 times to review the evidence for orthopaedic surgery, provide expert opinion and draft recommendations for the main committee to consider. The last two of those meetings were combined with main committee meetings.
2. The obstetric subgroup was chaired by Professor Beverley Hunt and comprised the obstetrician from the main committee, 3 co-opted members: consultant haematologist, consultant obstetrician and gynaecologist and a midwife. The group met twice to review the evidence for obstetrics, provide expert opinion and draft recommendations for the main committee to consider.

The main committee had the responsibility for final approval of all recommendations in the guideline.

Staff from the NGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information specialists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee.

3.3.1 What this guideline covers

Adults and young people aged 16 and over admitted to hospital or attending hospital for day procedures. For further details please refer to the scope in appendix A and the review questions in section 4.2.

3.3.2 What this guideline does not cover

People with suspected or confirmed venous thromboembolism (VTE)

3.3.3 Relationships between the guideline and other NICE guidance

Related NICE technology appraisals:

- [Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults](#). NICE technology appraisal 245 (2012)

- [Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults](#). NICE technology appraisal 157 (2008)

- [Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults](#). NICE technology appraisal 170 (2009)

- [Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism](#). NICE technology appraisal 341 (2015)

- [Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism](#). NICE technology appraisal 327 (2014)

- [Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism](#). NICE technology appraisal 354 (2015)

- [Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism](#). NICE technology appraisal 287 (2013)

Related NICE interventional procedure guidance:

- [Ultrasound-enhanced, catheter-directed thrombolysis for deep vein thrombosis](#). NICE interventional procedure guidance 523 (2015)

- [Ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism](#). NICE interventional procedure guidance 524 (2015)

Related NICE medical technologies guidance:

- [The geko device for reducing the risk of venous thromboembolism](#). NICE medical technology guidance 19 (2014)

Related NICE guidelines:

- [Caesarean section](#). NICE clinical guideline 132 (2011)

- [Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)](#). NICE clinical guideline 68 (2008)

- [Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing](#). NICE clinical guideline 144 (2012)

Related NICE guidance currently in development:

- [Betrixaban for preventing venous thromboembolism in people hospitalised for acute medical conditions](#). NICE technology appraisal ID913. Publication expected September 2018

- [Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. NICE clinical guideline GID-NG10087](#). Publication expected September 2019

4   Methods

This chapter sets out in detail the methods used to review the evidence and to develop the recommendations that are presented in subsequent chapters of this guideline. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2014 version.[126]

Section 4.1 lists the assumptions made in this guideline. Sections 4.2 to 4.4 describe the process used to identify and review clinical evidence (summarised in Figure 1), sections 4.3 and 4.5 describe the process used to identify and review the health economic evidence, and section 4.6 describes the process used to develop recommendations.

Figure 1:   Step-by-step process of review of evidence in the guideline
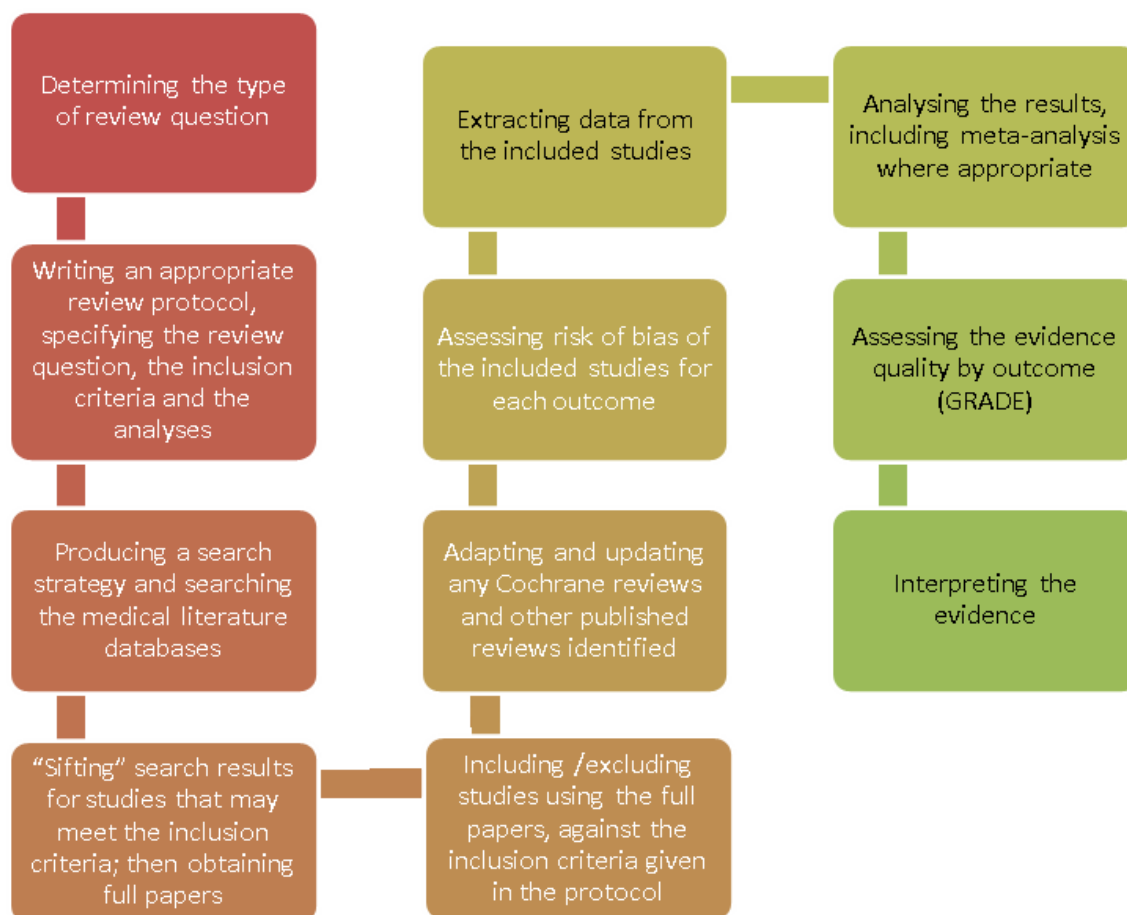
4.1   Assumptions made in this guideline

The committee has produced this guideline based upon available evidence from randomised trials. Many of these trials report the clinical effectiveness of interventions for primary VTE prophylaxis based on their effectiveness in reducing the risk of DVT (both symptomatic and asymptomatic). The committee acknowledges that this is a 'surrogate' endpoint which is frequently employed in randomised controlled trials (RCTs).

There are several difficulties when considering the outcomes of pulmonary embolism (PE) or symptomatic DVT:

1.   These are infrequent events – few trials exist that are adequately powered to truly answer the issue. Therefore, large trials (or numbers of trials) are needed to demonstrate an effect.

2. Few trials that report PE have made the diagnosis using objective methods (clinical diagnosis being unreliable).

3. Many trials that report PE or symptomatic DVT as an outcome measure have also assessed all included patients for asymptomatic DVT. Trial protocols usually dictate that patients in whom an asymptomatic DVT is detected are removed from the trial and anticoagulation is given, and hence a PE or symptomatic DVT may be prevented that would have occurred in the usual clinical setting.

DVT is a usual precursor of PE, fatal PE and post-thrombotic syndrome (PTS), although the aetiology and development of the diseases have not yet been fully elucidated. Although asymptomatic DVT is, by definition, covert these thrombi can become pulmonary embolisms and are a clinically useful endpoint for a trial. The committee therefore consider it an appropriate approach to evaluate both asymptomatic and symptomatic DVT when looking at the effectiveness of prophylaxis strategies. Clinical detection of DVT is unreliable and also fails to detect asymptomatic events, hence only trials that assess all patients for DVT using objective methods are included.

4.2 Developing the review questions and outcomes

Review questions were developed using a PICO framework (population, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews; and using a framework of population, setting and context for qualitative reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the committee. The review questions were drafted by the NGC technical team and refined and validated by the committee. The questions were based on the key clinical areas identified in the scope (appendix A).

A total of 42 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: **Review questions**

Chapter	Type of review	Review questions	Outcomes
1.1	Prognostic risk tools	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?	• Discrimination (sensitivity, specificity, predictive values; c-statistic) • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) Other statistical measures: for example, D statistic, R^2 statistic and Brier points
1.2	Prognostic risk tools	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?	• Discrimination (sensitivity, specificity, predictive values; c-statistic) • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration)

Chapter	Type of review	Review questions	Outcomes
			Other statistical measures: for example, D statistic, R^2 statistic and Brier points
1.3	Intervention	How clinically and cost effective are risk assessment tools at reducing the rate of VTE in patients who are admitted to hospital?	Critical: • All-cause mortality (up to 90 days from hospital discharge) • 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)
2.1	Prognostic risk tools	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?	• Discrimination (sensitivity, specificity, predictive values; c-statistic) • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) Other statistical measures: for example, D statistic, R^2 statistic and Brier points
2.2	Prognostic risk tools	What is the accuracy of individual risk assessment or predication tools in	• Discrimination (sensitivity, specificity, predictive values; c-

Chapter	Type of review	Review questions	Outcomes
		predicting the likelihood of major bleeding or the risk of bleeding in patients who are having day procedures (including surgery and chemotherapy) at hospital?	statistic) • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) Other statistical measures: for example, D statistic, R^2 statistic and Brier points
2.3	Intervention	How clinically and cost effective are risk assessment tools at reducing the rate of VTE in patients who are having day procedures (including surgery and chemotherapy) at hospital?	Critical: • All-cause mortality (up to 90 days from hospital discharge) • 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)
3.1	Prognostic risk tools	How effective is reassessment of people who are admitted to hospital?	• Discrimination (sensitivity, specificity, predictive values; c-statistic) • Area under the ROC curve (c-statistic) • Predicted risk versus observed

Chapter	Type of review	Review questions	Outcomes
			risk (calibration)
			Other statistical measures: for example, D statistic, R^2 statistic and Brier points
3.2	Prognostic risk tools	How effective is reassessment of people who are having day procedures at hospital?	• Discrimination (sensitivity, specificity, predictive values; c-statistic) • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) Other statistical measures: for example, D statistic, R^2 statistic and Brier points
4.1	Prognostic risk tools	What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE or 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?	• Discrimination (sensitivity, specificity, predictive values; c-statistic) • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) Other statistical measures: for example, D statistic, R^2 statistic and Brier points
	Intervention	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?	Critical: • All-cause mortality (up to 90 days from hospital discharge) • 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

Chapter	Type of review	Review questions	Outcomes
		43	• 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)
	Prognostic risk tools	How effective is reassessment of the risk of VTE and/or bleeding of pregnant women who are admitted to hospital or midwife units?	• Discrimination (sensitivity, specificity, predictive values; c-statistic) • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) Other statistical measures: for example, D statistic, R^2 statistic and Brier points
5.1	Qualitative	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?	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
8.1	Intervention	What is the effectiveness of weight based dose-adjustment strategies of LMWH compared to fixed dose strategies of LMWH for people who are obese?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • Health-related quality of life (validated scores only) (up to

Chapter	Type of review	Review questions	Outcomes
		44	90 days from hospital discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study)
9.1	Intervention	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 antiplatelet agents)?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
10.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) when interrupting anticoagulation therapy?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from

Chapter	Type of review	Review questions	Outcomes
		45	hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
11.1	Intervention	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 antiplatelet agents)?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)

Chapter	Type of review	Review questions	Outcomes
12.1	Intervention	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?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
13.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for acutely ill medical patients admitted to hospital?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from

Chapter	Type of review	Review questions	Outcomes
		47	• hospital discharge) • 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)
14.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with cancer having day procedures?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
15.1	Intervention	What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for people with central venous catheters?	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) • Pulmonary embolism (up to 90 days from hospital discharge)

Chapter	Type of review	Review questions	Outcomes
		48	• Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
16.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are having palliative care?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
17.1	Intervention	What is the effectiveness of different pharmacological and mechanical	Critical outcomes: • All-cause mortality (up to 90

Chapter	Type of review	Review questions	Outcomes
		prophylaxis strategies (alone or in combination) for people admitted to intensive care units?	days from hospital discharge) • Deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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) • Line associated thrombosis (duration of study)
18.1	Intervention	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)?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • Health-related quality of life (validated scores only) (up to 90 days from hospital

Chapter	Type of review	Review questions	Outcomes
			discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study)
19.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with psychiatric disorders?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
21.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people with lower limb immobilisation?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge)

Chapter	Type of review	Review questions	Outcomes
		51	**Important outcomes:** • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
22.1	Intervention	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?	**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) • Pulmonary embolism (symptomatic and asymptomatic) (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) **Important outcomes:** • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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) • Infection (duration of study)
23.1	Intervention	What is the effectiveness of different	Critical outcomes:

Chapter	Type of review	Review questions	Outcomes
		pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective hip replacement?	• All-cause mortality (up to 90 days from hospital discharge) • Deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) • Surgical site haematoma (up to 45 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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) • Infection (duration of study)
24.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective knee replacement surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) • Surgical site haematoma (up to 45 days from hospital discharge)

Chapter	Type of review	Review questions	Outcomes
		53	Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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) • Infection (duration of study)
25.1	Intervention	What is the effectiveness of difference pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having non-arthroplasty knee surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
26.1	Intervention	What is the effectiveness of different pharmacological and mechanical	Critical outcomes: • All-cause mortality (up to 90

Chapter	Type of review	Review questions	Outcomes
		prophylaxis strategies (alone or in combination) in people having foot and ankle surgery? 54	days from hospital discharge) • Deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
27.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) in people having upper limb surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • Health-related quality of life

Chapter	Type of review	Review questions	Outcomes
		55	(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)
28.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing spinal surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
29.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing	Critical outcomes: • All-cause mortality (up to 90 days from hospital discharge) • Deep vein thrombosis

Chapter	Type of review	Review questions	Outcomes
		intracranial surgery?	(symptomatic and asymptomatic) (up to 90 days from hospital discharge) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
30.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with spinal injury?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • Health-related quality of life (validated scores only) (up to 90 days from hospital discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study)

Chapter	Type of review	Review questions	Outcomes
			• Technical complications of mechanical interventions (duration of study)
31.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with major trauma?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
32.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing abdominal surgery (gastrointestinal, gynaecological, urological)?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from

Chapter	Type of review	Review questions	Outcomes
		58	hospital discharge) • 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)
33.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing bariatric surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
34.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing cardiac surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge)

Chapter	Type of review	Review questions	Outcomes
		59	• Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
35.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing thoracic surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)

Chapter	Type of review	Review questions	Outcomes
36.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing vascular surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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)
37.1	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing oral or maxillofacial surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • Health-related quality of life (validated scores only) (up to 90 days from hospital

Chapter	Type of review	Review questions	Outcomes
			discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study) • Cerebral sinus thrombosis (up to 30 days from hospital discharge)
37.2	Intervention	What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing ear, nose or throat (ENT) surgery?	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) • Pulmonary embolism (up to 90 days from hospital discharge) • Major bleeding (up to 45 days from hospital discharge) • Fatal PE (up to 90 days from hospital discharge) Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge) • 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 (up to 30 days from hospital discharge)

4.3 Searching for evidence

4.3.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the

NICE guidelines manual 2014.[126] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed. The searches for prophylaxis and risk assessment tools questions were conducted in Medline, Embase, and The Cochrane Library. Medline, Embase, CINAHL, Current Nursing and Allied Health Literature and PsycINFO were searched for the patient information question. All searches were updated on 19 June 2017. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking committee members to highlight any additional studies. Searches were quality assured by a second information specialist before being run. The questions, the study types applied, the databases searched and the years covered can be found in appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov)
- NHS Evidence Search (www.evidence.nhs.uk).

All references sent by stakeholders were considered. Searching for unpublished literature was not undertaken. The NGC and NICE do not have access to drug manufacturers' unpublished clinical trials results, so the clinical evidence considered by the committee for pharmaceutical interventions may be different from that considered by the MHRA and European Medicines Agency for the purposes of licensing and safety regulation.

As an update of the previous VTE guideline, date limits were set at the final search dates for the 2008 guideline. Papers identified prior to the 2008 date limit were selected from the previous guideline database and are listed as additional records identified through other sources.

4.3.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the venous thromboembolism population in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). Additionally, the search was run on Medline and Embase using a health economic filter, from January 2013, to ensure recent publications that had not yet been indexed by the economic databases were identified. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed.

The health economic search strategies are included in appendix G. All searches were updated on 19 June 2017. No papers published after this date were considered.

4.4 Identifying and analysing evidence of effectiveness

Research fellows conducted the tasks listed below, which are described in further detail in the rest of this section:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.

- Reviewed full papers against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (review protocols are included in appendix C).

- Critically appraised relevant studies using the appropriate study design checklist as specified in the NICE guidelines manual.[126] Prognostic risk tool studies were critically appraised using the Prediction study Risk of Bias Assessment Tool (PROBAST) checklist (see appendix H in the NICE guidelines manual 2014).[126] Qualitative studies were critically appraised using the GRADE CERQual approach for rating confidence in the body of evidence as a whole and using an NGC checklist for the methodological limitations section of the quality assessment.

- Extracted key information about interventional study methods and results using 'Evibase', NGC's purpose-built software. Evibase produces summary evidence tables, including critical appraisal ratings. Key information about non-interventional study methods and results was manually extracted onto standard evidence tables and critically appraised separately (evidence tables are included in appendix H).

- Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:

  o Randomised data were meta-analysed where appropriate and reported in GRADE profile tables.

  o Data from non-randomised studies were presented as a range of values in GRADE profile tables or meta-analysed if appropriate.

  o Prognostic data were meta-analysed where appropriate and reported in GRADE profile tables.

  o Diagnostic data studies were meta-analysed where appropriate or presented as a range of values in adapted GRADE profile tables

  o Qualitative data were synthesised across studies and presented as summary statements with accompanying GRADE CERQual ratings for each review finding.

- A sample of a minimum of 10% of the abstract lists of the first 3 sifts by new reviewers and those for complex review questions (for example, prognostic reviews) were double-sifted by a senior research fellow and any discrepancies were rectified. All of the evidence reviews were quality assured by a senior research fellow. This included checking:

  o papers were included or excluded appropriately

  o a sample of the data extractions

  o correct methods were used to synthesise data

  o a sample of the risk of bias assessments.

4.4.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in appendix N. The committee was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- Adults and young people (16 years and older) admitted to hospital or community mental health hospital and units or midwife units.

The key population exclusion criteria were:

- People in community settings and hospices, except when continuing prophylaxis that has been started in hospital.
- People with suspected or confirmed venous thromboembolism.
- People having secondary prevention for VTE.

Conference abstracts were not included in any of the review. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

4.4.2   Type of studies

Randomised trials, non-randomised studies, and other observational studies (including prognostic studies) were included in the evidence reviews as appropriate.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. If non-randomised intervention studies were considered appropriate for inclusion (for example, where no randomised evidence was available for the risk assessment tool reviews) the committee stated a priori in the protocol that either certain identified variables must be equivalent at baseline or else the analysis had to adjust for any baseline differences. If the study did not fulfil either criterion it was excluded. Please refer to the review protocols in appendix C for full details on the study design of studies selected for each review question.

For prognostic review questions, prospective and retrospective cohort studies were included. Case–control studies were not included.

Where data from non-randomised studies were included, the results for each outcome were presented separately for each study or meta-analysed if appropriate.

4.4.3   Relative value of different outcomes

Across reviews the committee prioritised all-cause mortality, deep vein thrombosis (DVT; symptomatic and asymptomatic), pulmonary embolism (PE), fatal PE and major bleeding as critical outcomes. PE is a debilitating event and, if it does not lead to death (fatal PE), it will considerably impact the person's quality of life. In the long term, PE can lead to chronic thromboembolic pulmonary hypertension (CTEPH) which is a costly, chronic illness which has a negative impact on quality of life. The committee acknowledge that DVT is a surrogate outcome, however there is an underlying assumption that DVT is a precursor of PE and it is an outcome used in the majority of VTE studies. There are difficulties relying on PE data alone. PE is a rarer event, and therefore much larger numbers of patients are required to demonstrate a clinically important effect. Trials that assess for PE also assess for DVT and trial protocols dictate that if DVT is identified anticoagulation should be initiated. Therefore it is likely that many trials underestimate PE rates. For these reasons the committee considered it was appropriate to use DVT as an endpoint alongside PE. The committee did not want to rely solely on symptomatic DVT as this is a subjective outcome and may be determined differently by different clinical specialties. For instance in orthopaedic studies such as elective knee replacement there may be pain in the leg for other reasons, making the distinction between symptomatic and asymptomatic DVT problematic. DVT (symptomatic and asymptomatic) can both lead to complications of future PE which are the most serious clinical events, both can also lead to post-thrombotic syndrome in the longer term. Major bleeding is the primary adverse event associated with pharmacological prophylaxis. The committee wished to highlight the importance of balancing the risk of VTE against the risk of bleeding when considering pharmacological prophylaxis.

4.4.4 Methods of combining clinical studies

4.4.4.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted using Cochrane Review Manager (RevMan5)[159] software to combine the data given in all studies for each of the outcomes of interest for the review question.

For some questions stratification was used, and this is documented in the individual review question protocols (see appendix C).

4.4.4.1.1 Analysis of different types of data

Dichotomous outcomes

Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate risk ratios (relative risk, RR) for the binary outcomes, which included:

- All-cause mortality
- Deep vein thrombosis (symptomatic and asymptomatic)
- Pulmonary embolism (PE)
- Fatal PE
- Major bleeding
- Clinically relevant non-major bleeding
- Health-related quality of life
- Heparin-induced thrombocytopenia (HIT)
- Technical complications of mechanical interventions.

The absolute risk difference was also calculated using GRADEpro[62] software, using the median event rate in the control arm of the pooled results.

For binary variables where there were zero events in either arm or a less than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events. For binary variables where there were zero-events in both arms, risk difference is presented in the forest plots.

Continuous outcomes

Continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. These outcomes included:

- heath-related quality of life using the Visual Analogue Score(VAS).

Where the studies within a single meta-analysis had different scales of measurement, standardised mean differences were used (providing all studies reported either change from baseline or final values rather than a mixture of both); each different measure in each study was 'normalised' to the standard deviation value pooled between the intervention and comparator groups in that same study.

The means and standard deviations of continuous outcomes are required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% confidence intervals (95% CI) were reported, and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) [159] software. Where p values were reported as 'less than', a conservative

approach was undertaken. For example, if a p value was reported as 'p≤0.001', the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (version 5.1.0, updated March 2011) were applied.

4.4.4.1.2 *Generic inverse variance*

If a study reported only the summary statistic and 95% CI the generic-inverse variance method was used to enter data into RevMan5.[159] If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro.[62] If multivariate analysis was used to derive the summary statistic but no adjusted control event rate was reported no absolute risk difference was calculated.

4.4.4.1.3 *Heterogeneity*

Statistical heterogeneity was assessed for each meta-analysis estimate. Initially this was done through visual inspection of the forest plots, investigating the variability of the point estimates and the overlap of the confidence intervals. If there was little overlap between confidence intervals for at least two of the trial, or there was a wide spread between point estimates, then we further investigated by considering heterogeneity statistics. The chi-squared test for significance at p<0.1 or an I-squared (I^2) inconsistency statistic (with an I-squared value of more than 50% indicating significant heterogeneity) as well as the distribution of effects. Where significant heterogeneity was present, predefined subgrouping of studies was carried out as determined a priori in the protocols (appendix C).

If the subgroup analysis resolved heterogeneity within all of the derived subgroups, then each of the derived subgroups were adopted as separate outcomes (providing at least 1 study remained in each subgroup). Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Any subgroup differences were interpreted with caution as separating the groups breaks the study randomisation and as such is subject to uncontrolled confounding.

If all predefined strategies of subgrouping were unable to explain statistical heterogeneity within each derived subgroup based on visual inspection of the subgroup forest plots and consideration of the heterogeneity statistics (e.g. I^2), then a random effects (DerSimonian and Laird) model was employed to the entire group of studies in the meta-analysis. It was assumed this model would be a better fit for the data if the heterogeneity suggests that it is unlikely that the data are estimating the same true effect. A random-effects model assumes a distribution of populations, rather than a single population. This leads to a widening of the confidence interval around the overall estimate, thus providing a more realistic interpretation of the true distribution of effects across more than 1 population. If, however, the committee considered the heterogeneity was so large that meta-analysis was inappropriate, then the results were described narratively.

4.4.4.2   Network meta-analysis

A network meta-analysis (NMA) was conducted for the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people having elective hip replacement surgery, elective knee replacement surgery and abdominal surgery (gastrointestinal, gynaecological, urological). This type of analysis simultaneously compares multiple treatments in a single meta-analysis, preserving the randomisation of RCTs included in the reviews of direct comparisons trials. The aim of the NMA was to include all relevant evidence in order both to answer questions on the clinical effectiveness of interventions when no direct comparison was available and to give a ranking of treatments in terms of efficacy. The output was expressed as the probability of each VTE prophylaxis treatment being the best for an outcome and as effect estimates for how much each treatment is better than the other treatments included in the network.

A hierarchical Bayesian NMA was performed using the software WinBUGS version 1.4.3. We used statistical models for fixed and random effects that allowed inclusion of multi-arm trials and accounts for the correlation between arms in the trials with any number of trial arms. The model was based on original work from the University of Bristol.[200] The checklist 'Evidence Synthesis of Treatment Efficacy in Decision Making: A Reviewer's Checklist'[3] was completed.

As it is the case for ordinary pairwise meta-analysis, NMA may be conducted using either fixed-effects or random-effects models. For pairwise meta-analysis, a fixed-effects model was used in the first instance. For the networks set up in our NMA, both fixed- and random-effect models were performed. These models were then compared based on residual deviance and deviance information criteria (DIC). The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed.

Heterogeneity was assessed in the results of the random-effects model by using the method described by Dias[50] which compares the size of the treatment effect to the extent of between-trials variation. This method tries to answer the question of what is the reasonable confidence interval of the log odds ratio of an outcome for the prediction of the confidence interval of the log odds ratio of the same outcome of a future trial of infinite size.

Inconsistency in the networks was tested by comparing any available direct and indirect treatment comparison and testing the null hypothesis that the indirect evidence was not different from the direct evidence on the risk ratio scale using the normal distribution. Inconsistency was identified if the mean estimates (mean risk ratios) of the direct comparisons were outside the confidence intervals of the risk ratios as generated from the NMA output.

There were 2 main outputs from the NMA:

- estimated risk ratios (RRs) (with their 95% credible intervals) were calculated for comparisons of the direct and indirect evidence
- a ranking of treatments compared to baseline groups (presented as the median rank and its 95% credible intervals).

4.4.4.3 Data synthesis for risk prediction rules

Evidence reviews on risk prediction rules or risk prediction tool results were presented separately for discrimination and calibration. The discrimination data were analysed according to the principles of data synthesis for diagnostic accuracy studies. An 'at risk' result using a risk assessment tool was found if the person had values of the measured quantity above or below a threshold value, and different thresholds could be used. Predictive accuracy measures used in the analysis were: area under the receiver operating characteristics (ROC) curve (AUC), and, for different cut-off points (if appropriate), sensitivity and specificity. The cut-off point of a risk assessment tool is defined as the value at which the test can best differentiate between those most at risk of the particular outcome being assessed (VTE or major bleeding) and those less at risk. In practice this varies amongst studies. If a risk tool demonstrates a high sensitivity then very few people at increased risk will be missed (few false negatives). For example, a risk assessment tool with a sensitivity of 97% will only miss identifying 3% of people who are at increased risk. Conversely, if a risk assessment tool demonstrates a high specificity then few people at low risk will be incorrectly flagged as at increased risk (few false positives). For example, a test with a specificity of 97% will only incorrectly identify 3% of people who are not at increased risk as at risk. For this guideline, sensitivity was considered more important than specificity due to the consequences of an incorrect risk assessment (false negative result).Coupled forest plots of sensitivity and specificity with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5. [159] In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given, or else were derived from raw data or calculated from the set of test accuracy statistics.

Meta-analysis was conducted where appropriate, that is, when 3 or more studies were available per threshold. Predictive accuracy for the studies was pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random-effects approach in WinBUGS software. [200] The advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the 2 statistics. Other advantages of this method have been described elsewhere.[158, 187, 188] The bivariate method uses logistic regression on the true positives, true negatives, false positives and false negatives reported in the studies. Overall sensitivity and specificity and confidence regions were plotted (using methods outlined by Novielli 2010.[139]) Pooled sensitivity and specificity and their 95% CIs were reported in the clinical evidence summary tables. For scores with fewer than 3 studies, median sensitivity and the paired specificity were reported where possible.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots

Calibration data such as r-squared (R2), if reported, were presented separately to the discrimination data. The results were presented for each study separately along with the quality rating for the study. Inconsistency and imprecision were not assessed.

4.4.4.4 Data synthesis for qualitative study reviews

The main findings for each included paper were identified and thematic analysis methods were used to synthesise this information into broad overarching themes which were summarised into the main review findings. The evidence was presented in the form of a narrative summary detailing the evidence from the relevant papers and how this informed the overall review finding plus a statement on the level of confidence for that review finding. Considerable limitations and issues around relevance were listed. A summary evidence table with the succinct summary statements for each review finding was produced including the associated quality assessment.

4.4.5 Appraising the quality of evidence by outcomes

4.4.5.1 Intervention reviews

The evidence for outcomes from the included RCTs and, where appropriate, non-randomised intervention studies, were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro[62]) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2.

Table 2: **Description of quality elements in GRADE for intervention studies**

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional or assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.

Quality element	Description
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm) and thus be imprecise.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an overestimate of the effectiveness of that outcome.
Other issues	Sometimes randomisation may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be taken into account. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given below. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

4.4.5.1.1 *Risk of bias*

The main domains of bias for RCTs are listed in Table 3. Each outcome had its risk of bias assessed within each study first. For each study, if there were no risks of bias in any domain, the risk of bias was given a rating of 0. If there was risk of bias in just 1 domain, the risk of bias was given a 'serious' rating of −1, but if there was risk of bias in 2 or more domains the risk of bias was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account the weighting of studies according to study precision. For example if the most precise studies tended to each have a score of −1 for that outcome, the overall score for that outcome would tend towards −1.

Table 3:   Principle domains of bias in randomised controlled trials

Limitation	Explanation
Selection bias (sequence generation and allocation concealment)	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of: • knowledge of that participant's likely prognostic characteristics, and • a desire for one group to do better than the other.
Performance and detection bias (lack of blinding of patients and healthcare professionals)	Patients, caregivers, those adjudicating or recording outcomes, and data analysts should not be aware of the arm to which patients are allocated. Knowledge of the group can influence: • the experience of the placebo effect • performance in outcome measures • the level of care and attention received, and • the methods of measurement or analysis all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from an unaccounted for loss of data beyond a certain level (a differential of 10% between groups). Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If

Limitation	Explanation
	the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules. • Use of unvalidated patient-reported outcome measures. • Lack of washout periods to avoid carry-over effects in crossover trials. • Recruitment bias in cluster-randomised trials.

The assessment of risk of bias differs for non-randomised intervention studies, as they are inherently at high risk of selection bias. For this reason, GRADE requires that non-randomised evidence is initially downgraded on the basis of study design, starting with a rating of −2. This accounts for selection bias and so non-randomised intervention studies are not downgraded any further on that domain. Non-randomised evidence was assessed against the remaining domains used for RCTs in Table 3, and downgraded further as appropriate.

4.4.5.1.2 *Indirectness*

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for the risk of bias, each outcome had its indirectness assessed within each study first. For each study, if there were no sources of indirectness, indirectness was given a rating of 0. If there was indirectness in just 1 source (for example in terms of population), indirectness was given a 'serious' rating of −1, but if there was indirectness in 2 or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome by taking into account study precision. For example, if the most precise studies tended to have an indirectness score of −1 each for that outcome, the overall score for that outcome would tend towards −1.

4.4.5.1.3 *Inconsistency*

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in the underlying treatment effect, which may be due to differences in populations, settings or doses. When heterogeneity existed within an outcome (chi-squared p<0.1, or I^2>50%), but no plausible explanation could be found, the quality of evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of −1 if the I^2 was 50–74%, and a 'very serious' score of −2 if the I^2 was 75% or more.

If inconsistency could be explained based on pre-specified subgroup analysis (that is, each subgroup had an I^2<50%), the committee took this into account and considered whether to make separate recommendations on new outcomes based on the subgroups defined by the assumed explanatory factors. In such a situation the quality of evidence was not downgraded for those emergent outcomes.

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

4.4.5.1.4   *Imprecision*

The criteria applied for imprecision were based on the 95% CIs for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. If either end of the 95% CI of the overall estimate of effect crossed 1 of the MID lines, imprecision was regarded as serious and a 'serious' score of −1 was given. This was because the overall result, as represented by the span of the confidence interval, was consistent with 2 interpretations as defined by the MID (for example, both no clinically important effect and clinical benefit were possible interpretations). If both MID lines were crossed by either or both ends of the 95% CI then imprecision was regarded as very serious and a 'very serious' score of −2 was given. This was because the overall result was consistent with all 3 interpretations defined by the MID (no clinically important effect, clinical benefit and clinical harm). This is illustrated in Figure 2. As for inconsistency, since the imprecision score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

The position of the MID lines is ideally determined by values reported in the literature. 'Anchor-based' methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or 'anchoring' them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, a MID for an outcome could be defined by the minimum amount of change in that outcome necessary to make patients feel their quality of life had 'significantly improved'. MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life or health. For binary variables, any MIDs reported in the literature will inevitably be based on expert consensus, as such MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, and so are not amenable to patient-centred 'anchor' methods.

In the absence of values identified in the literature, the alternative approach to deciding on MID levels is the 'default' method, as follows:

- For categorical outcomes the MIDs were taken to be RRs of 0.75 and 1.25. For 'positive' outcomes such as 'patient satisfaction', the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm.

- For mortality any change was considered to be clinically important and the imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect, that is whether the result was consistent with both benefit and harm.

- For continuous outcome variables the MID was taken as half the median baseline standard deviation of that variable, across all studies in the meta-analysis. Hence the MID denoting the minimum clinically significant benefit was positive for a 'positive' outcome (for example, a quality of life measure where a higher score denotes better health), and negative for a 'negative' outcome (for example, a visual analogue scale [VAS] pain score). Clinically significant harms will be the converse of these. If baseline values are unavailable, then half the median comparator group standard deviation of that variable will be taken as the MID.

- If standardised mean differences have been used, then the MID will be set at the absolute value of +0.5. This follows because standardised mean differences are mean differences normalised to the pooled standard deviation of the 2 groups, and are thus effectively expressed in units of 'numbers of standard deviations'. The 0.5 MID value in this context therefore indicates half a standard deviation, the same definition of MID as used for non-standardised mean differences.

The default MID value was subject to amendment after discussion with the committee. If the committee decided that the MID level should be altered, after consideration of absolute as well as relative effects, this was allowed, provided that any such decision was not influenced by any bias towards making stronger or weaker recommendations for specific outcomes.

For this guideline, no appropriate MIDs for continuous or dichotomous outcomes were found in the literature, and so the default method was adopted with no cases of the committee altering the values used.

Figure 2: Illustration of precise and imprecise outcomes based on the 95% CI of dichotomous outcomes in a forest plot (Note that all 3 results would be pooled estimates, and would not, in practice, be placed on the same forest plot)
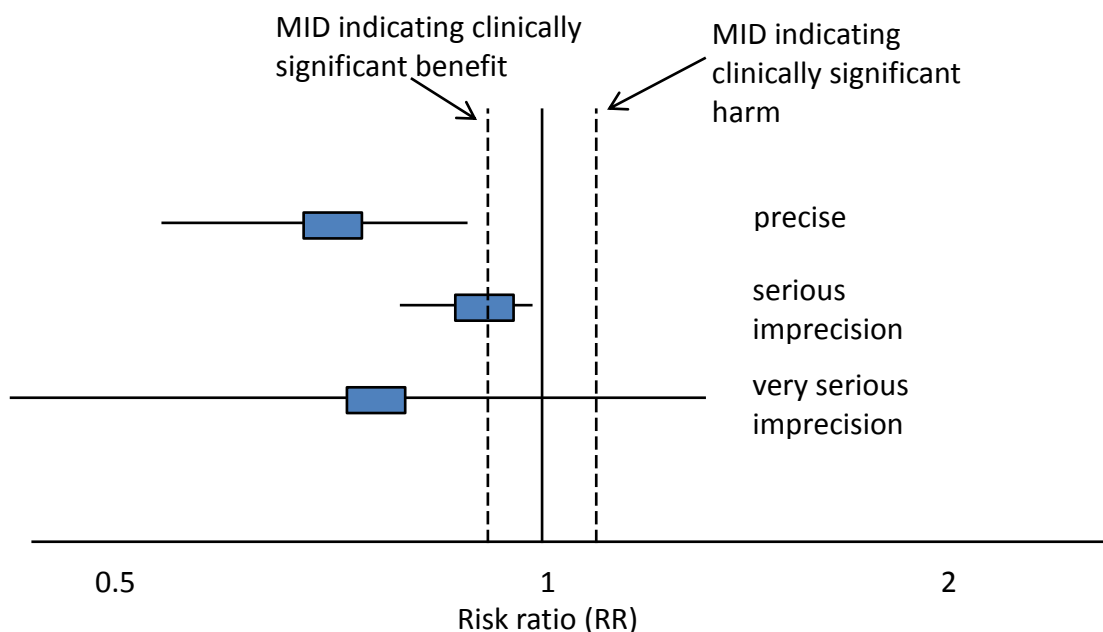
4.4.5.1.5 *Overall grading of the quality of clinical evidence*

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores (0, −1 or −2) from each of the main quality elements were summed to give a score that could be anything from 0 (the best possible) to −8 (the worst possible). However scores were capped at −3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. All RCTs started as High and the overall quality became Moderate, Low or Very Low if the overall score was −1, −2 or −3 points respectively. The significance of these overall ratings is explained in Table 4. The reasons for downgrading in each case were specified in the footnotes of the GRADE tables.

Non-randomised intervention studies started at Low, and so a score of −1 would be enough to take the grade to the lowest level of Very Low. Non-randomised intervention studies could, however, be upgraded if there was a large magnitude of effect or a dose-response gradient.

Table 4:   Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Level	Description
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.4.5.2 Prognostic reviews

Risk of bias and applicability of evidence for prognostic risk data were evaluated by study using the Prediction study Risk of Bias Assessment Tool (PROBAST) checklist (see appendix H in the NICE guidelines manual 2014).[126] Risk of bias and applicability in risk prediction studies in PROBAST consists of 4 domains:

- patient selection
- predictors
- outcome
- analysis.

If data were meta-analysed, the quality for pooled studies was presented. If the data were not pooled, then a quality rating was presented for each study.

4.4.5.2.1 *Inconsistency*

Inconsistency for calibration outcomes was assessed as for intervention studies. Inconsistency for discrimination outcomes was assessed by inspection of the primary measure (sensitivity) using the point estimates and 95% Cis of the individual studies on the forest plots. Particular attention was placed on values above or below 50% (prediction based on chance alone) and the threshold set by the committee (the threshold above which it would be acceptable to recommend a test). For example, the committee might have set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by 1 increment if the individual studies varied across 2 areas (for example, 50–90% and 90–100%) and by 2 increments if the individual studies varied across 3 areas (for example, 0–50%, 50–90% and 90–100%).

4.4.5.2.2 *Imprecision*

In meta-analysed calibration outcomes, or for non-pooled outcomes, the position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. For discrimination outcomes, the judgement of precision was based on visual inspection of the confidence region around the summary sensitivity and specificity point from the meta-analysis, if a meta-analysis was conducted. Where a meta-analysis was not conducted, imprecision was assessed according to the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

4.4.5.2.3 *Overall grading*

Quality rating started at High for prospective studies, and each major limitation brought the rating down by 1 increment to a minimum grade of Very Low, as explained for interventional reviews. For prognostic reviews prospective cohort studies with a multivariate analysis are regarded as the gold standard because RCTs are usually inappropriate for these types of review for ethical or pragmatic reasons. Furthermore, if the study is looking at more than 1 risk factor of interest then randomisation would be inappropriate as it can only be applied to 1 of the risk factors.

4.4.5.3 Qualitative reviews

Review findings from the included qualitative studies were evaluated and presented using the 'Confidence in the Evidence from Reviews of Qualitative Research' (CERQual) Approach developed by the GRADE-CERQual Project Group, a subgroup of the GRADE Working Group.

The CERQual Approach assesses the extent to which a review finding is a reasonable representation of the phenomenon of interest (the focus of the review question). Each review finding was assessed for each of the 4 quality elements listed and defined below in Table 5.

Table 5: Description of quality elements in GRADE-CERQual for qualitative studies

Quality element	Description
Methodological limitations	The extent of problems in the design or conduct of the included studies that could decrease the confidence that the review finding is a reasonable representation of the phenomenon of interest. Assessed at the study level using an NGC checklist.
Coherence	The extent to which the reviewer is able to identify a clear pattern across the studies included in the review.
Relevance	The extent to which the body of evidence from the included studies is applicable to the context (study population, phenomenon of interest, setting) specified in the protocol.
Adequacy	The degree of the confidence that the review finding is being supported by sufficient data. This is an overall determination of the richness (depth of analysis) and quantity of the evidence supporting a review finding or theme.

Details of how the 4 quality elements (methodological limitations, coherence, relevance and adequacy) were appraised for each review finding are given below.

4.4.5.3.1 *Methodological limitations*

Each review finding had its methodological limitations assessed within each study first using an NGC checklist. Based on the degree of methodological limitations studies were evaluated as having minor, moderate or severe limitations. The questions to be answered in the checklist below included:

- Was qualitative design an appropriate approach?
- Was the study approved by an ethics committee?
- Was the study clear in what it sought to do?
- Is the context clearly described?
- Is the role of the researcher clearly described?
- Are the research design and methods rigorous?
- Was the data collection rigorous?
- Was the data analysis rigorous?
- Are the data rich?
- Are the findings relevant to the aims of the study?
- Are the findings and conclusions convincing?

The overall assessment of the methodological limitations of the evidence was based on the primary studies contributing to the review finding. The relative contribution of each study to the overall review finding and of the type of methodological limitation(s) were taken into account when giving an overall rating.

4.4.5.3.2 *Coherence*

Coherence is the extent to which the reviewer is able to identify a clear pattern across the studies included in the review, and if there is variation present (contrasting or disconfirming data) whether

this variation is explained by the contributing study authors. If a review finding in 1 study does not support the main finding and there is no plausible explanation for this variation, then the confidence that the main finding reasonably reflects the phenomenon of interest is decreased. Each review finding was given a rating of minor, moderate or major concerns about coherence.

4.4.5.3.3 Relevance

Relevance is the extent to which the body of evidence from the included studies is applicable to the context (study population, phenomenon of interest, setting) specified in the protocol. As such, relevance is dependent on the individual review and discussed with the committee. Relevance is categorised in 3 ways: partial relevance, indirect relevance and no concerns about relevance.

4.4.5.3.4 Adequacy

The judgement of adequacy is based on the confidence of the finding being supported by sufficient data. This is an overall determination of the richness (depth of analysis) and quantity of the evidence supporting a review finding or theme. Rich data provide sufficient detail to gain an understanding of the theme or review finding, whereas thin data do not provide enough detail for an adequate understanding. Quantity of data is the second pillar of the assessment of adequacy. For review findings that are only supported by 1 study or data from only a small number of participants, the confidence that the review finding reasonable represents the phenomenon of interest might be decreased. As with richness of data, quantity of data is review dependent. Based on the overall judgement of adequacy, a rating of no concerns, minor concerns, or substantial concerns about adequacy was given.

4.4.5.3.5 Overall judgement of the level of confidence for a review finding

GRADE-CERQual is used to assess the body of evidence as a whole through a confidence rating representing the extent to which a review finding is a reasonable representation of the phenomenon of interest. The 4 components (methodological limitations, coherence, relevance and adequacy) are used in combination to form an overall judgement. GRADE-CERQual uses 4 levels of confidence: high, moderate, low and very low confidence. The significance of these overall ratings is explained in Table 6. Each review finding starts at a high level of confidence and is downgraded based on the concerns identified in any 1 or more of the 4 components. Quality assessment of qualitative reviews is a subjective judgement by the reviewer based on the concerns that have been noted. A detailed explanation of how such a judgement had been made was included in the narrative summary.

Table 6:   Overall level of confidence for a review finding in GRADE-CERQual

Level	Description
High confidence	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest.
Moderate confidence	It is likely that the review finding is a reasonable representation of the phenomenon of interest.
Low confidence	It is possible that the review finding is a reasonable representation of the phenomenon of interest.
Very low confidence	It is not clear whether the review finding is a reasonable representation of the phenomenon of interest.

4.4.6   Assessing clinical importance

The committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk

differences (ARDs) using GRADEpro[62] software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews (the same absolute risk considered to represent a clinically important benefit/harm for a certain outcome in one review would be the same for that outcome in another review). For the critical outcome of all-cause mortality any reduction or increase was considered to be clinically important.

This assessment was carried out by the committee for each critical outcome, and an evidence summary table was produced to compile the committee's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

4.4.7 Clinical evidence statements

Clinical evidence statements are summary statements that are included in each review chapter, and which summarise the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments).
- A description of the overall quality of the evidence (GRADE overall quality).

4.5 Identifying and analysing evidence of cost effectiveness

The committee is required to make decisions based on the best available evidence of both clinical effectiveness and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost. However, the committee will also need to be increasingly confident in the cost effectiveness of a recommendation as the cost of implementation increases. Therefore, the committee may require more robust evidence on the effectiveness and cost effectiveness of any recommendations that are expected to have a substantial impact on resources; any uncertainties must be offset by a compelling argument in favour of the recommendation. The cost impact or savings potential of a recommendation should not be the sole reason for the committee's decision.[126]

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

4.5.1 Literature review

The health economists:

- Identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using economic evaluations checklists as specified in the NICE guidelines manual.[126]

- Extracted key information about the studies' methods and results into health economic evidence tables (included in appendix J).

- Generated summaries of the evidence in NICE health economic evidence profile tables (included in the relevant chapter for each review question) – see below for details.

4.5.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 2001 and studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see Table 7 below and the economic evaluation checklist (appendix H of the NICE guidelines manual[126]) and the health economics review protocol in appendix D.

When no relevant health economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the committee to inform the possible economic implications of the recommendations.

4.5.1.2 NICE health economic evidence profiles

NICE health economic evidence profile tables were used to summarise cost and cost-effectiveness estimates for the included health economic studies in each review chapter. The health economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual.[126] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio (ICER) for the base case analysis in the study, as well as information about the assessment of uncertainty in the analysis. See Table 7 for more details.

When a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[141]

Table 7: Content of NICE health economic evidence profile

Item	Description
Study	Surname of first author, date of study publication and country perspective with a reference to full information on the study.
Applicability	An assessment of applicability of the study to this guideline, the current NHS situation and NICE decision-making:[a]
	• Directly applicable – the study meets all applicability criteria, or fails to meet 1 or more applicability criteria but this is unlikely to change the conclusions about cost

Item	Description
	effectiveness.
	• Partially applicable – the study fails to meet 1 or more applicability criteria, and this could change the conclusions about cost effectiveness.
	• Not applicable – the study fails to meet 1 or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study:[a]
	• Minor limitations – the study meets all quality criteria, or fails to meet 1 or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness.
	• Potentially serious limitations – the study fails to meet 1 or more quality criteria, and this could change the conclusions about cost effectiveness.
	• Very serious limitations – the study fails to meet 1 or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Information about the design of the study and particular issues that should be considered when interpreting it.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects (usually in £ per QALY gained).
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in appendix H of the NICE guidelines manual[126]

4.5.2 Undertaking new health economic analysis

As well as reviewing the published health economic literature for each review question, as described above, new health economic analysis was undertaken by the health economist in selected areas. Priority areas for new analysis were agreed by the committee after formation of the review questions and consideration of the existing health economic evidence.

The committee identified the prophylaxis strategies for people undergoing elective total hip replacement and elective total knee replacement as the highest priority areas for original health economic modelling. The committee considered the decision to offer thromboprophylaxis for these populations and the choice of the thromboprophylaxis strategy as likely to have substantial economic impact; given the large size of these populations. Additionally, the committee acknowledged that there is variation in practice in terms of the choice of a prophylaxis strategy and different NICE products that offer guidance regarding this including CG92 and three technology appraisals (TAs): TA157, TA170 and TA245.[124, 127, 129, 131] Hence, the committee considered that it would be important to address the need for a standardised advice and a single source to be used by clinicians. The full rationale for prioritising these questions is given in the respective chapters: elective hip replacement (chapter 23) and elective knee replacement (chapter 24).

The following general principles were adhered to in developing the cost-effectiveness analyses:

• Methods were consistent with the NICE reference case for interventions with health outcomes in NHS settings.[126, 132]

- The committee was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NGC.

Full methods for the cost-effectiveness analysis for prophylaxis strategies for people undergoing elective total hip and elective total knee replacement surgeries are described in appendix P.

4.5.3   Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that committees should consider when judging whether an intervention offers good value for money.[128] In general, an intervention was considered to be cost effective (given that the estimate was considered plausible) if either of the following criteria applied:

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[128]

When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.5.4   In the absence of health economic evidence

When no relevant published health economic studies were found, and a new analysis was not prioritised, the committee made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

4.6   Developing recommendations

Over the course of the guideline development process, the committee was presented with:
- Evidence tables of the clinical and health economic evidence reviewed from the literature. All evidence tables are in Appendices H and J.
- Summaries of clinical and health economic evidence and quality (as presented in chapters 5–40).

- Forest plots and summary ROC curves (appendix L).
- A description of the methods and results of the cost-effectiveness analyses undertaken for the guideline (appendix P).

Recommendations were drafted on the basis of the committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the committee took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the committee's values and preferences), and the confidence the committee had in the evidence (evidence quality). Secondly, the committee assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical and health economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the committee, or on the occasion of the risk assessment recommendations, by informal voting methods. The committee also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 4.6.1 below).

The committee considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The committee focused on the following factors in agreeing the wording of the recommendations:
- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weaker recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see section 9.2 in the NICE guidelines manual[126]).

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.6.1 Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

4.6.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

4.6.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.6.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

4.6.5 Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

5 Risk assessment for medical, surgical and trauma patients

5.1 Introduction

Risk assessment is a crucial part of deciding whether to give prophylaxis. When making a judgement on using an intervention to reduce the risk of VTE, it is important to consider:

- the reason for admission to hospital (for example, a surgical procedure or a medical problem) and factors individual to the patient concerned (for example age, gender, pre-existing medical conditions and medication use) that influence the likelihood of VTE
- the likely treatment benefit from the specific prophylactic intervention
- the possible harmful effect of the intervention.

Pharmacological methods are widely used for VTE prophylaxis. These come with the potential harm of increasing the risk of bleeding. Major bleeding is clearly a threat to life, but under some circumstances a low volume bleed can be a very major complication. A few millilitres of bleeding into the brain, or compressing the spinal cord within the vertebral canal can cause death or permanent neurological damage.

The risk assessment recommendations from the last version of the guideline (CG92) aligned with a tool produced by the Department of Health which has since become known as the National VTE Risk Assessment Tool.[73] In 2010 NICE introduced a quality standard requiring all patients to receive an assessment of VTE and bleeding risk on admission using the clinical risk assessment criteria described in the National Tool. [130] Subsequently, the Department of Health Commissioning for Quality and Innovation (CQUIN) payment framework linked the uptake of risk assessment with payments. Since 2012 over 90% of hospital admissions were risk assessed for VTE using the National Tool.

This current version of the guideline reviewed the evidence for existing risk assessment tools or checklists for VTE and bleeding. The reviews covered:

- both the predictive accuracy and clinical and cost effectiveness of tools
- tools that included VTE and bleeding risk together in a tool or as separate tools
- tools that grouped all populations together or separated them into reasons for attending hospital, for example, surgical patients, medical inpatients or patients undergoing day procedures.

After admission or a procedure at hospital a person's medical condition will usually change. As a consequence of this change their risk of VTE and bleeding may also change. The last version of the guideline (CG92) recommended patients were reassessed every 24 hours. This update reviewed the evidence for the effectiveness of reassessment of VTE and bleeding risk to establish if this time point was appropriate for some or all patients.

5.2 Accuracy of risk assessment tools for VTE in hospital admissions

5.2.1 Review question: What is the accuracy of individual risk assessment or prediction tools in predicting the likelihood of VTE in a patient who is admitted to hospital?

For full details see review protocol in appendix C.

Table 8:   PICO characteristics of review question

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?
Population	Adults and young people (aged 16 or over) admitted to hospital
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)
Outcomes (in terms of predictive test accuracy, calibration)	Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values) • 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 Exclusions: derivation studies

5.2.2   Clinical evidence

Twenty-two studies evaluating 13 risk assessment models were included in the review, [10, 18, 63, 64, 68, 75, 77, 79, 105, 106, 133, 140, 146, 147, 150, 164, 165, 175, 189, 190, 201, 202] these are summarised in Table 9 below. See also the study selection flow chart in appendix E, study evidence tables in appendix H, and excluded studies list in appendix N. Full details of the tools included in this review are provided in the clinical evidence tables in appendix H.

Seven studies focused on VTE risk assessment in hospitalised medical patients,[63, 133, 165, 189, 202] including one specifically on hospitalised cancer patients.[150] Ten focused on surgical patients,[10, 18, 68, 77, 106, 140, 146, 175, 190, 201] three focused on trauma patients,[75, 79, 164] and study each on VTE risk assessment in people after a stroke[105] and people with thermal (burn) injuries.[147]

The risk assessment models identified by the literature included the Caprini risk assessment model, the Kucher score, the Geneva risk score, the predictive (4 factor) IMPROVE tool, the Intermountain risk assessment model, the Khorana Score, the Padua Prediction Score and the Trauma Embolic Scoring System (TESS).

Table 9:   Summary of studies included in the review

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Risk assessment in medical patients					
Grant 2016 [63]	Caprini Score	n= 63,548 Hospitalised medical patients USA	VTE, hospital associated (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	n= 670 (1.05%)	Retrospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
			based on positive findings via compression Doppler ultrasound or venography, PE was confirmed via computed tomography (CT) scan, ventilation perfusion scan or pulmonary angiography Sensitivity and specificity		
Greene 2016 [64]	Kucher Score Padua Prediction Score International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) Intermountain risk assessment model	n= 63,548 Acutely ill, hospitalised medical patients USA	VTE, hospital associated (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 scan or pulmonary angiography C-statistic	n= 670 (1.05%)	Prospective cohort
Nendaz 2014 [133]	Geneva Risk Score Padua Prediction Score	n=1478 Acutely medically ill patients Age: 65%(>60 years); 44% (≥ 70 years) Gender (male to female ratio): not reported Switzerland	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. Sensitivity Specificity	n= 30 (2.3%)	Prospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
			PPV NPV NLR		
Patell 2017 [150]	Khorana Score	n=2780 Hospitalised cancer patients Age, median (range): 62 (19-98) years. Gender (male to female ratio): 1545: 1235 USA	VTE: based on ICD-9 codes Sensitivity and specificity calculated using prevalence and risk tool data reported.	n=106 (3.8%)	Retrospective cohort
Rothberg 2011 [165]	Unnamed (Rothberg 2011)	n= 48, 540 Medical patients Age: 18-49 years; 12.9%, 50-64 years, 21.1%, 65+ years 66.0% Gender (male to female ratio): 41.6 :58.4 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% USA	VTE, hospital acquired (3 days after hospitalisation - end point not reported): 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	n= 223 (0.46%)	Retrospective cohort
Vardi 2013 [189]	Padua Prediction Score	n= 1080 People with sepsis admitted to internal medicine departments Age (mean± SD): 74.68± 16.15	VTE (time point: For in hospital VTE our assumption is that it is an event between 48 hours after admission and discharge) Includes DVT or PE. Diagnosis of DVT by Duplex ultrasound or	n=14 (1.29%)	Prospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		Gender (male to female ratio): 1.09:1 Israel	computer tomography (CT) and diagnosis of PE was based on a positive CT angiography (CTA) or a high-probability ventilation perfusion scan. C-statistic		
Woller 2011 [202]	Intermountain risk assessment model Kucher Score	n=46856 (for both risk tools) Medically ill patients Age (mean): 61.14 years Gender (male to female ratio): 1.17:1 USA	VTE (90 days): not defined. C-statistic	n=2109 (4.5%)	Retrospective cohort
Risk assessment in surgical patients					
Bahl 2010 [10]	Caprini risk assessment model	n=8216 Undergoing major surgery (>45 minutes) 88.16%; general 67%, vascular 16%, 17% urologic) 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 USA	VTE (30 days): not defined. C-statistic Hosmer-Lemeshow test	n=118 (1.44%)	Retrospective cohort
Bilimoria 2013 [18]	American College of Surgeons National Surgical Quality Improvement Programme (ACS NSQIP) Universal Surgical Risk Calculator	Colon surgery n= 88,334 Undergoing colorectal surgery Age and gender: no details of validation cohort USA	VTE (30 days): not defined. C-statistic Brier score	Colon surgery n=3508 (4%)	Retrospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Hachey 2016 [68]	Caprini risk assessment model	n=232 People undergoing lung cancer resections: lobectomy (84.5%), segmenectomy (8.2%), pneumonectomy (7.3%) Age: Adults (with VTE mean 63.83±10.2 years, without VTE mean 64.36±11 years) Gender (male to female ratio): 100:132 USA	VTE (60 days): any PE or DVT identified via clinical imaging studies (computed tomography pulmonary angiogram or duplex ultrasound) and treated with therapeutic anticoagulation or inferior vena cava filter. Sensitivity Specificity C-statistic PPV NPV Hosmer-Lemeshow test	n=12 (5.2%)	Retrospective cohort
Hewes 2015 [77]	Modified Caprini score	n=70 Undergoing oesophagectomy for oesophageal cancer Age: with VTE mean 64.9±6.4, without VTE mean 61.6±11.7 Gender (male to female ratio): 58:12 USA	VTE (1-60 days): defined as any thromboembolic event diagnosed by appropriate imaging findings and treated with therapeutic anticoagulation or inferior vena cava filter. Sensitivity Specificity PPV NPV C-statistic Hosmer-Lemeshow test	n=10 (14.3%)	Retrospective cohort
Lobastov 2016 [106]	Caprini risk assessment model	n=140 High-risk patients who underwent emergency abdominal (48%) or cranial/spinal (52%) surgery already receiving pharmacological prophylaxis Age, mean (SD): 69.2 (12.2)	"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.	n=39 (27.9%)	Retrospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		Gender (male to female ratio): 68:72 Russia	Sensitivity Specificity C-statistic		
Obi 2015 [140]	Caprini risk assessment model	n=4844 Critically ill surgical patients (surgical ICU). Including general surgery, transplant, urology, and orthopaedic patients and patients with respiratory failure requiring extracorporeal membrane oxygenation 82% major operative procedures 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 USA	VTE (time point unclear): defined as patients with DVT or PE which occurred during the patient's initial hospital admission. 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 C-statistic Hosmer-Lemeshow test	DVT n= 308 (6.4%) PE n=79 (1.6%)	Retrospective cohort
Pannucci 2014 [146]	Unnamed (Pannucci 2014)	n=3576 Postsurgical patients (details of surgical procedures not provided for validation sample) Overall age: ≥ 60 years:	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,	n= 50 (1.40%)	Prospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		62% Overall gender (male to female ratio): 1:1.36 USA	tibial, or popliteal veins. PE included clots in the pulmonary vasculature. All VTE events were diagnosed using an objective imaging study. C-statistic		
Shaikh 2016 [175]	Caprini risk assessment model	n=1598 People undergoing plastic surgery Age, mean (range): 49.9 (14-86) years Gender (male to female ratio): 308:1290 BMI, mean (range): 28.2 (15.9-77.5) kg/m2 USA	VTE: DVT/PE composite: not defined Sensitivity Specificity	n=24 (1.5%)	Retrospective cohort
Vaziri 2017 [190]	American College of Surgeons National Surgical Quality Improvement Programme (ACS NSQIP) Universal Surgical Risk Calculator	n=1006 People undergoing neurosurgery Age not reported. Gender (male/female): 460/546 USA	VTE: no further details provided c-statistic	n=13 (1.29%)	Retrospective cohort
Winoker 2017 [201]	American College of Surgeons National Surgical Quality Improvement Programme (ACS NSQIP) Universal Surgical Risk Calculator	n=300 People undergoing urological surgery, specifically robot-assisted partial nephrectomy Age (%): <65 (63.7); 65-73 (26.3); 75-84 (9.7); ≥85 (0.3) years Gender (male to female ratio): 185:115	VTE: no further details provided c-statistic Brier score	n=1 (0.33%)	Retrospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		BMI (%): <18.5 (0.7); 18.5-24.9 (13.3); 25-29.9 (39.7); ≥30 (46.3) kg/m2 USA			
Risk assessment in people with trauma					
Hegsted 2013 [75]	Risk Assessment Profile (RAP)	n=2281 People with trauma Age (mean): 45.2 years Gender (male to female ratio): 2.33:1 USA	DVT (time point unclear): not defined PE (time point unclear): detected by computed tomography-angiography or post-mortem examination Sensitivity Specificity PPV NPV	DVT n= 239 (10.5%) PE n=34 (1.5%)	Retrospective cohort
Ho 2014 [79]	Trauma Embolic Scoring System (TESS)	n=357 People with trauma Chest injury: 61.9% Abdominal injury: 29.1% Spinal fractures: 43.4% Pelvic fractures: 32.8% Lower limb fractures: 38.4% 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 Australia	VTE (time point unclear): DVT and PE confirmed by colour Doppler compression ultrasound and computed tomography pulmonary angiography or post mortem examination. Sensitivity Specificity PPV NPV Hosmer-Lemeshow test	Overall VTE: n=74 (21%) Fatal PE: n= 16 (4.48%) Non-fatal PE: 22 (6.16% DVT: 47 (13.17%)	Retrospective cohort
Rogers 2012 [164]	Trauma Embolic Scoring System (TESS)	n=234,032 People with trauma Injury type: blunt 86.9%, burn 2.5%, penetrating 10.6% (missing data for	VTE (unclear time point): included deep vein thrombosis (DVT) or pulmonary embolism (PE) DVT: The formation,	n=4,881 (1.4%)	Retrospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		26,928) Age: <30 years 40.9%, 30-64 years 41.7%, ≥65 years 17.4% Gender (male to female ratio): 1.92:1 USA	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. 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. Sensitivity Specificity C-statistic PPV NPV Hosmer-Lemeshow test		
Risk assessment in people post-stroke					
Liu 2014 [105]	Post-stroke DVT Prediction System	n=287 Acute stroke patients	DVT (14±3 days): Diagnosis of DVT if complete compression duplex	n=30 (10.6%)	Prospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		Age: ≥65 years 58.2% Gender (male to female ratio: 1.68:1) China	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) C-statistic		
Risk assessment in people with thermal injuries (burns)					
Pannucci 2012 [147]	Simple Venous Thromboembolism Risk Scoring Tool	n= 5761 People with thermal injury Age (mean): 45.6 years Gender (male to female ratio): 2.33:1 USA and Canada	VTE (time point unclear: not defined) C-statistic	n=559 (9.7%)	Retrospective cohort

5.2.3 Discrimination

5.2.3.1 VTE

5.2.3.1.1 *General medical patients*

Table 10: Clinical evidence profile: risk tools for predicting VTE in general medical patients

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Risk tool: Caprini risk assessment model										
Caprini risk assessment model Cut-off 5	1	63548	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	69.7 (66-73)	50.3 (50-51)	-	VERY LOW
Caprini risk assessment model Cut-off 7	1	63548	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	42.7 (39-47)	74.7 (74-75)	-	VERY LOW
Caprini risk assessment model Cut-off 9	1	63548	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	18.5 (16-22)	89.0 (89-89)	-	VERY LOW
Risk tool: Geneva Risk Score										
Geneva Risk Score High risk ≥3	1	1478	Serious[a]	No serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	90 (73.5-97.9)	35.3 (32.8-37.8)	-	MODERATE
Risk tool: IMPROVE (Predictive version - four factors available at admission)										
IMPROVE High risk ≥2	1	63548	Serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	-	-	0.570 (0.565-0.576)	LOW

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Risk tool: Intermountain										
Intermountain High risk ≥1	2	110404	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	-	-	0.611 (0.605-0.618) 0.843 (0.833-0.852)	VERY LOW
Risk tool: Kucher score										
Kucher Score High risk ≥4	2	110404	Serious [a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	-	-	0.563 (0.558-0.568) 0.683 (0.673-0.691)	LOW
Risk tool: Padua Prediction score										
Padua Prediction Score High risk ≥4	3	66106	Very serious[a]	No serious inconsistency[b]	No serious indirectness[c]	Serious imprecision[d]	73.3 (54.1-87.7)	51.9 (49.3-54.5)	0.60 (0.59-0.61) 0.58 (0.43-0.73)	VERY LOW
Risk tool: Unnamed (Rothberg 2011)										
(Unnamed)	1	48540	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	-	-	0.75 (0.71-0.78)	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias

(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability

(d) Imprecision was assessed according to the range of point estimates of the primary measure (sensitivity where possible, or if missing then c-statistic). The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

General medical –oncology inpatients

Table 11: Clinical evidence profile: risk tools for predicting VTE in hospitalised cancer patients

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Khorana Score High-risk ≥3	1	2780	Very serious[a]	No serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	18.9 (12-28)	87.2 (86-88)	-	LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) *Risk of bias was assessed using the PROBAST checklist items relating to risk of bias*

(b) *Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).*

(c) *Indirectness was assessed using the PROBAST checklist items relating to applicability*

(d) *Imprecision was assessed according to the range of point estimates of the primary measure (sensitivity where possible, or if missing then c-statistic). The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.*

5.2.3.1.2 *Surgical patients*

Mixed surgical patients

Table 12: Clinical evidence profile: risk tools for predicting VTE in mixed surgical patients

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Caprini score	2	13060	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	Not estimable	-	-	0.585 0.698	VERY LOW
Unnamed risk model (Pannucci 2014)	1	3576	Very serious[a]	No serious inconsistency[b]	No serious indirectness[c]	Not estimable	-	-	0.70	LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias

(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability

(d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

Colorectal surgery patients

Table 13: Clinical evidence profile: risk tools for predicting VTE in people undergoing colorectal surgery

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
American College of Surgeons National Surgical Quality Improvement Programme: Universal Surgical Risk Calculator	1	88,334	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	Not estimable	-	-	0.7203	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias

(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability

(d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

People undergoing lung cancer resections

Table 14: Clinical evidence profile: risk tools for predicting VTE in people undergoing surgery for lung cancer

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Caprini score Moderate to high risk >5	1	232	Very serious [a]	No serious inconsistency [b]	No serious indirectness [c]	No serious imprecision [d]	100 (100 – 100)	7.2 (4.1 – 11)	-	LOW
Caprini score Cut-off >7 (chosen to ensure 100% sensitivity)	1	232	Very serious [a]	No serious inconsistency [b]	No serious indirectness [c]	No serious imprecision [d]	100 (100 – 100)	31.4 (25 – 37.3)	-	LOW
Caprini score High risk >9	1	232	Very serious [a]	No serious inconsistency [b]	No serious indirectness [c]	Very serious imprecision [d]	83.3 (58.3 – 100)	60.5 (54.4 – 67.3)	0.72	VERY LOW
Caprini score Cut-off >10 (chosen for highest c-statistic)	1	232	Very serious [a]	No serious inconsistency [b]	No serious indirectness [c]	Very serious imprecision [d]	75 (50 -100)	69.6 (64.4 – 76.4)	0.73	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias

(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability

(d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

Oesophageal cancer surgery patients

Table 15: Clinical evidence profile: risk tools for predicting VTE in people undergoing oesophagectomy for oesophageal cancer

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Modified Caprini score (>15) [Hewes 2015]	1	70	Very serious[a]	No serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	100 (100 – 100)	66.7 (55 – 78.3)	0.818 (0.7111 – 0.908)	LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias

(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability

(d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

People undergoing plastic surgery

Table 16: Clinical evidence profile: risk tools for predicting VTE in people undergoing plastic surgery

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Caprini score Cut-off ≥5	1	1598	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	71 (49-87)	39 (37-42)	-	VERY LOW
Caprini score Cut-off ≥6	1	1598	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	Very serious imprecision[d]	58 (37-78)	60 (58-63)	-	VERY LOW
Caprini score Cut-off ≥9	1	1598	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	17 (5-37)	93 (92-94)	-	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias

(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability

(d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

People undergoing neurosurgery

Table 17:   Clinical evidence profile: risk tools for predicting VTE in already known high-risk people undergoing neurosurgery

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
American College of Surgeons National Surgical Quality Improvement Programme: Universal Surgical Risk Calculator	1	1006	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	Not estimable	-	-	0.767	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) *Risk of bias was assessed using the PROBAST checklist items relating to risk of bias*

(b) *Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).*

(c) *Indirectness was assessed using the PROBAST checklist items relating to applicability*

People undergoing urological surgery – robot-assisted partial nephrectomy

Table 18: Clinical evidence profile: risk tools for predicting VTE in already known high-risk people undergoing urological surgery – robot-assisted partial nephrectomy

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
American College of Surgeons National Surgical Quality Improvement Programme: Universal Surgical Risk Calculator	1	300	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	Not estimable	-	-	0.670	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias

(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability

High-risk patients undergoing emergency abdominal surgery or neurosurgery

Table 19: Clinical evidence profile: risk tools for predicting VTE in already known high-risk people undergoing emergency abdominal surgery or neurosurgery

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Caprini score Cut-off ≥10.5	1	140	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	95 (83-99)	73 (64-82)	0.87 (0.811 – 0.93)	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias
(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).
(c) Indirectness was assessed using the PROBAST checklist items relating to applicability
(d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

5.2.3.1.3 People with trauma

Table 20: Clinical evidence profile: risk tools for predicting VTE in people with trauma

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
TESS High risk <9	1	357	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	97 (91-99)	27 (22-32)	0.71 (0.65-0.77)	VERY LOW
TESS Risk cut off >5	1	234,032	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	77.4 (76-79)	75.6 (75-76)	0.84 (0.83-0.84)	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias
b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).
c) Indirectness was assessed using the PROBAST checklist items relating to applicability
d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

5.2.3.1.4 *People with thermal injuries (burns)*

Table 21: Clinical evidence profile: risk tools for predicting VTE in thermally injured (burned) people

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Risk Scoring Tool for Thermally Injured Patients	1	5761	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	Not estimable	-	-	0.750	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.
(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias
(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).
(c) Indirectness was assessed using the PROBAST checklist items relating to applicability
(d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

5.2.3.2 DVT

5.2.3.2.1 *People with trauma*

Table 22: Clinical evidence profile: risk tools for predicting DVT in people with trauma

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
RAP Moderate risk cut-off 5 to ≤14	1	2281	Serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	82 (77-87)	57 (55-59)	-	LOW
RAP High risk cut-off >14	1	2281	Serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	15 (11-20)	97 (97-98)	-	LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity was this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) *Risk of bias was assessed using the PROBAST checklist items relating to risk of bias*

(b) *Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).*

(c) *Indirectness was assessed using the PROBAST checklist items relating to applicability*

(d) *Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.*

5.2.3.2.2 People who have had a stroke

Table 23: Clinical evidence profile: risk tools for predicting DVT in stroke patients

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Post stroke DVT Prediction System	1	287	Very serious[a]	No serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	-	-	0.65 (0.59-0.70)	LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) *Risk of bias was assessed using the PROBAST checklist items relating to risk of bias*

(b) *Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a*

test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).

(c) *Indirectness was assessed using the PROBAST checklist items relating to applicability*

(d) *Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20- 40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.*

5.2.3.3 PE (fatal and non-fatal PE)

5.2.3.3.1 *People with trauma*

Table 24: Clinical evidence profile: risk tools for predicting fatal and non-fatal PE in trauma patients

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
TESS High risk <9	1	357	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	97 (87-99)	24 (20-29)	0.67 (0.59-0.75)	VERY LOW
RAP Cut-off 5 to ≤14	1	2281	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	71 (55-86)	53 (51-56)	-	VERY LOW
RAP Cut-off >14	1	2281	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	12 (10-23)	96 (95-97)	-	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) *Risk of bias was assessed using the PROBAST checklist items relating to risk of bias*

(b) *Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).*

(c) *Indirectness was assessed using the PROBAST checklist items relating to applicability*

(d) *Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.*

5.2.3.4 Fatal PE

5.2.3.4.1 *People with trauma*

Table 25: Clinical evidence profile: risk tools for predicting fatal PE in trauma patients

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
TESS High risk <9	1	357	Very serious[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	100 (81-100)	20 (13-28)	-	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) *Risk of bias was assessed using the PROBAST checklist items relating to risk of bias*

(b) *Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).*

(c) *Indirectness was assessed using the PROBAST checklist items relating to applicability*

(d) *Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.*

5.2.4   Calibration

5.2.4.1   VTE

5.2.4.1.1 *Surgical patients*

Mixed surgical patients

Table 26: Clinical evidence profile: risk tools for predicting VTE in mixed surgical patients

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R² (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R² (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
Caprini score	2	130 60	Very serious[a]	Serious indirectness[b]	Not estimable	-	0.607 0.609	-	-	VERY LOW

(a) Risk of bias was assessed using the PROBAST checklist.
(b) Downgraded by 1 increment as the definition of target condition does not match protocol

Colorectal surgery patients

Table 27: Clinical evidence profile: risk tools for predicting VTE in people undergoing colorectal surgery

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R² (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
ACS NSQIP Universal Surgical Risk Calculator	1	88,334	Very serious[a]	Serious indirectness[b]	Not estimable	-	-	0.0218	-	VERY LOW

(a) Risk of bias was assessed using the PROBAST checklist.
(b) Downgraded by 1 increment as the definition of target condition does not match protocol

People undergoing lung cancer resections

Table 28: Clinical evidence profile: risk tools for predicting VTE in people undergoing surgery for lung cancer

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R² (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
Caprini score High risk >5	1	232	Very serious[a]	No serious indirectness	Not estimable	-	0.61	-	-	LOW

(a) Risk of bias was assessed using the PROBAST checklist.

Oesophageal cancer surgery patients

Table 29: Clinical evidence profile: risk tools for predicting VTE in people undergoing oesophagectomy for oesophageal cancer

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R^2 (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
Caprini score High risk >5	1	70	Very serious[a]	No serious indirectness	Not estimable	-	10.282 (0.113)	-	-	LOW

(a) Risk of bias was assessed using the PROBAST checklist.

People undergoing urological surgery – robot-assisted partial nephrectomy

Table 30: Clinical evidence profile: risk tools for predicting VTE in people undergoing urological surgery – robot-assisted partial nephrectomy

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R^2 (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
ACS NSQIP Universal Surgical Risk Calculator	1	300	Very serious[a]	Serious indirectness[b]	Not estimable	-	-	0.003327	-	VERY LOW

(a) Risk of bias was assessed using the PROBAST checklist.
(b) Downgraded by 1 increment as the definition of target condition does not match protocol

5.2.4.1.2 People with trauma

Table 31: Clinical evidence profile: risk tools for predicting VTE in trauma patients

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R^2 (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R^2 (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
TESS	2	234,389	Very serious[a]	Serious indirectness[b]	Not estimable	-	0.101 13.70	-	-	VERY LOW

(a) Risk of bias was assessed using the PROBAST checklist.
(b) Downgraded by 1 increment as the definition of target condition does not match protocol

5.2.4.2 PE (non-fatal and fatal PE)

5.2.4.2.1 *People with trauma*

Table 32: Clinical evidence profile: risk tools for predicting non-fatal and fatal PE in trauma patients

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R^2 (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
TESS cut off <9	1	357	Serious[a]	No serious indirectness	Not estimable	-	13.7	-	-	MODERATE

(a) Risk of bias was assessed using the PROBAST checklist.

5.2.4.3 Fatal PE

5.2.4.3.1 *People with trauma*

Table 33: Clinical evidence profile: risk tools for predicting fatal PE in trauma patients

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R2 (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
TESS Cut-off <9	1	357	Serious[a]	Serious indirectness[b]	Not estimable	-	13.7	-	-	LOW

(a) Risk of bias was assessed using the PROBAST checklist.

(b) *Downgraded by 1 increment as the definition of target condition does not match protocol*

5.2.5   Economic evidence

Published literature

No relevant health economic studies were identified.

See also the economic article selection flow chart in appendix F.

5.2.6   Evidence statements

Clinical

General medical patients

Evidence was available for seven tools that assessed VTE risk in general medical patients. Very low quality evidence from one study (n=63,548) that explored the predictive ability of the Caprini risk assessment model at three separate cut off points (5, 7 and 9) showed sensitivities at all thresholds did not reach the committee's pre-specified threshold for decision-making (80%). No c-statistic data was available for the Caprini RAM. Moderate quality evidence from one study (n=1478) showed that the Geneva Risk Score might be sensitive enough for consideration (90%) however the variance around this estimate dipped below the committee's decision-making threshold (95% CI 73.5-97.9) and the accompanying specificity (0.353 [0.328-0.378]) was much lower than the committee's decision-making threshold (60%). Low quality evidence from one study (n=63,548) showed that the predictive version of IMPROVE offered poor discrimination (c-statistic 0.570 [0.565-0.576]) with no corresponding sensitivity and specificity data reported. Very low quality evidence from two studies (n=110,404) using the Intermountain risk tool suggested that discrimination ranged from poor to moderate with reported c-statistics of 0.611 (0.605-0.618) and 0.843 (0.833-0.852), but no associated sensitivity and specificity data was reported in either study. Low quality evidence from two studies (110,404) suggested that the Kucher tool also offered poor discrimination with c-statistics of 0.563 (0.558-0.568) and 0.683 (0.673-0.691). Very low quality evidence from three studies (n=66,106) suggested the using the Padua Prediction Score with a cut-off of ≥4 produced sensitivity (0.733 [0.541-0.877]) and specificity (0.519 [0.493-0.545]) that did not reach the committee's pre-specified decision-making threshold; and showed poor discrimination with c-statistics of 0.60 (0.59-0.61) and 0.58 (0.43-0.73). Finally very low quality evidence from one study (n=48,540) showed that an unnamed risk tool (Rothberg 2011) showed moderate discrimination (0.75 [0.71-0.78]). A further eighth study was identified in the specific subgroup of hospitalised cancer patients. Low quality evidence from this study (n=2780) showed a sensitivity of 19% (12-28) and specificity of 87% (86-88) when using a high-risk cut-off of ≥3 to predict VTE.

One study (n=287) conducted with people who had had a stroke, provided low quality evidence that a Post-Stroke DVT Prediction System had moderate discrimination (c-stat 0.65 [0.59-0.70]) ability for predicting DVT in this particular population.

Surgical and trauma patients (including people with burn injuries)

Very low quality evidence from two studies (n=13,060) showed poor discrimination (c-statistics 0.585 and 0.698) for the Caprini RAM for predicting VTE in mixed surgical patients (Hosmer-Lemeshow test p values 0.607 and 0.609); and low quality evidence from one study (n=3,576) showed moderate discrimination for an unnamed risk model (Pannucci 2014) in a similar mixed surgical population. Very low quality evidence from one study (n=88,334) showed that the American College of Surgeons (ACS) National Surgical Quality Improvement Programme (NSQIP): Universal Surgical Risk Calculator showed moderate discrimination (0.7203) for predicting VTE in colorectal surgery patients (Brier score 0.0218). Low quality evidence from one study (n=232) looking at the Caprini RAM for predicting

VTE in people undergoing lung cancer resections showed moderate discrimination (0.72 and 0.73). At the lower cut-off points of 5 (H-L test p-value 0.61)and 7 the reported sensitivities were 100% however the associated specificities were well below the committee's pre-specified threshold for decision making (0.072 [0.041-0.11]; 0.314 [0.25-0.373]). At a cut-off of 9 the sensitivity and specificity estimates met the committee's thresholds (0.833 and 0.605) but the imprecision around these estimates fell below each of the decision-making thresholds. At a cut-off of 10 the primary measure for decision-making (sensitivity) did not meet the committee's threshold (0.75 [0.50-1.00]). Low quality evidence from one small study (n=70) showed moderate discrimination when using the modified Caprini RAM to predict VTE in oesophageal cancer surgery patients (c-statistic 0.818 [0.711-0.908]; H-L test [p-value]: 10.282 [0.113]). At a cut-off of >15 low quality evidence for this risk tool suggested 100% sensitivity and 66.7% specificity but the imprecision around the specificity measure dipped below the committee's pre-specified threshold for decision making (0.55-0.78). When using the Caprini RAM to predict VTE in people undergoing plastic surgery, very low quality evidence from one study (n=1598) showed no sensitivities that met the committee's pre-specified threshold when looking at multiple cut-offs (5, 6 and 9). Two studies explored the use of the ACS NQIP: universal surgical risk calculator for predicting VTE in patients undergoing neurosurgery (n=1006) and urological surgery (n=300). In both cases very low quality evidence was provided for the c-statistic only with no associated variance data. The c-statistic was showed moderate discrimination for the tool in the neurosurgical population (0.767) and poor discrimination in the urological surgery population (0.670; Brier score 0.003327). When looking at people already recognised at high-risk for VTE undergoing emergency abdominal or neurosurgery, low quality evidence from one study (n=140) showed moderate discrimination for the Caprini RAM (0.87 [0.81-0.93]) and sensitivity of 95% (83-99) and specificity of 73% (0.64-0.82) for predicting VTE at a cut-off of ≥10.5. Very low quality evidence from two studies suggested TESS showed moderate discrimination at predicting VTE in people with trauma (n=357, c-statistic 0.71 [0.65-0.77]; n=234032, c-stat 0.84 [0.83-0.84]). The smaller study reported sensitivity of 97% (91-99) and specificity of 27% (22-32) when using a cut-off of <9. The larger study reported sensitivity of 77% (76-79) and specificity of 76% (75-76) when using a cut-off of >5. One study (n=5761) provided very low quality evidence that a risk scoring tool for thermal injured patients showed moderate discrimination (0.750 [no CI reported]) for predicting VTE in people with burn injuries.

Low quality evidence from one study (n=2281) looked at RAP at two different thresholds for predicting DVT in people with trauma. The cut off of ≤14 showed sensitivity of 82% (77-87) and specificity of 57% (55-59). The cut-off of >14 showed sensitivity of 15% (11-20) and specificity of 97% (97-98). Very low quality evidence from this same study also reported the ability of RAP to predict PE and fatal PE. The cut off of ≤14 showed sensitivity of 71% (55-86) and specificity of 53% (51-56). The cut-off of >14 showed sensitivity of 12% (10-23) and specificity of 96% (95-97). Another study (n=357) provided very low quality evidence for the poor discrimination (0.67 [0.59-0.75]) of TESS at predicting the combination of PE and fatal PE in trauma patients. This study reported sensitivity of 97% (87-99) and specificity of 24% (20-29) for TESS at a cut-off of <9. When focusing specifically on fatal PE only, very low quality evidence showed sensitivity of 100% (81-100) and specificity of 20% (13-28) for TESS at a cut-off of <9.

Economic

No relevant economic evaluations were identified.

5.3 Accuracy of risk assessment tools for bleeding in hospital admissions

5.3.1 Review question: What is the accuracy of individual risk assessment or prediction tools in predicting the likelihood of major bleeding or the risk of bleeding in a patient who is admitted to hospital?

For full details see review protocol in appendix C.

Table 34: PICO characteristics of review question

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?
Population	Adults and young people (aged 16 or over) admitted to hospital
Risk tool	Derived and (externally or temporally) validated risk tools identified in literature
Target condition(s)	Major bleeding (up to 90 days)
Outcomes (in terms of predictive test accuracy, calibration)	Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values) • 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 Exclusions: derivation studies

5.3.2 Clinical evidence

One study evaluating the IMPROVE bleeding risk score was included in the review. [80] This is summarised in Table 35 below. See also the study selection flow chart in appendix E, study evidence tables in appendix H, and excluded studies list in appendix N.

Table 35: Summary of studies included in the review

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Hostler 2016 [80]	IMPROVE bleeding risk score	n=1668 Adults admitted for a medical illness. Age: <40: 234 (14%), 40-84: 1144 (68.6%), ≥85: 289 (17.3%) Gender (male to female ratio): 969:699 Ethnicity: not reported USA	Major bleeding at 14 days[a] Clinically relevant non-major bleeding at 14 days Based on UCD-9 codes and a haematocrit drop >6 points to identify patients who may have bled during admission. All bleeding events were confirmed by manual chart audit.	31 14	Prospective data collection with retrospective analysis.

(a) Raw data for 2x2 tables and calculation of sensitivity and specificity provided through author correspondence.

5.3.3 Discrimination

5.3.3.1 Major bleeding

Table 36: Clinical evidence profile: risk tools for predicting major bleeding in patients admitted to hospital

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	Area under the curve	Quality
IMPROVE bleeding risk score										
Major bleeding at 14 days	1	1668	Very serious[a]	-	No serious indirectness	No serious imprecision[b]	48 (27, 69)	78 (76, 81)	0.67 (0.57-0.77)	LOW
Major bleeding during hospitalisation	1	1668	Very serious[a]	-	No serious indirectness	No serious imprecision[b]	48 (30, 67)	78 (76, 81)	-	LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. Where sensitivity was not reported specificity values were used for the assessment, if these were not available the assessment was based on the C-statistic. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80%; specificity 60%.

(a) Risk of bias was assessed using the PROBAST checklist.

(b) Imprecision was assessed according to the range of point estimates of the primary decision measure (specificity). The evidence was downgraded by 1 increment when there was a 40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

5.3.4 Calibration

No calibration data reported.

5.3.5 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

5.3.6 Evidence statements

Clinical

Low quality evidence from one study (n=1668) suggested that calculating the IMPROVE bleeding risk score at admission was a poor predictor of major bleeding in medical inpatients (AUC 0.67 [95% CI 0.57-0.77]). The sensitivity of the IMPROVE bleeding risk score (0.48 [0.27-0.69]), the primary outcome for decision making, did not reach the committee's pre-specified thresholds (80%).

Economic

No relevant economic evaluations were identified.

5.4 Effectiveness of risk assessment tools in hospital admissions

5.4.1 Review question: How clinically and cost effective are risk assessment tools at reducing the rate of VTE in patients who are admitted to hospital?

For full details see review protocol in appendix C.

Table 37: PICO characteristics of review question

Population	Adults (aged 16 or over) admitted to hospital
Intervention(s)	Intervention: Derived and validated risk tool for predicting the risk of VTE/DVT/PE/major bleeding
	The Department of Health risk tool (not validated)
Comparison(s)	No risk tool, other risk tools
Outcomes	**Critical:**
	• All-cause mortality (up to 90 days from hospital discharge)
	• 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

5.4.2   Clinical evidence

As no randomised controlled trials were identified, observational studies were considered for inclusion in this review ; one retrospective cohort study[102], one prospective cohort study[59], and three before-and-after studies[24, 25, 162]; these are summarised in Table 38 below.

Three studies [24, 25,59] compared use of a risk tool with no risk tool (Department of Health risk tool, Caprini risk tool and the Padua prediction score). Two studies [102, 162] compared achieving the quality standard of 90% of admissions being assessed with the Department of Health risk tool with not achieving the quality standard.

Evidence from these studies is summarised in the clinical evidence summary below (Table 38). See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

Table 38:   Summary of studies included in the review: studies comparing use of risk tool versus no risk tool

Study	Intervention and comparison	Population	Outcomes
Cassidy 2014 [24]	Before and after study Before: Before development of the standardised program, no VTE prevention guidelines were formally used (2009). 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 After: Post-implementation (July 2011-June 2012). 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. Standardised VTE prophylaxis regimens were	Before implementation n=1,569 After implementation n=1,323 People undergoing general or vascular surgery, including people admitted to an ICU Age: Not reported Gender (male to female ratio): Not reported USA	DVT (30 days):new diagnosis of venous thrombosis, confirmed by imaging study or autopsy, which is treated with anticoagulation or placement of vena cava filter PE (30 days): new diagnosis of a new blood clot in a pulmonary artery, which is confirmed by imaging or autopsy.

Study	Intervention and comparison	Population	Outcomes
	created and linked to 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. Mobilisation program was also implemented, encouraging mobilisation of patients.		
Catterick 2014 [25]	Before and after study Before: 1 year before the implementation of Department of Health risk tool (2009) After: Two years after the implementation of Department of Health risk tool (2010/11)	n= not reported All people admitted to NHS hospitals in England. Age: Not reported Gender (male to female ratio): Not reported UK	VTE-related mortality (90 days) VTE-related readmission (30 days) VTE-related readmission (90 days) VTE: defined using ICD-10 codes used by the UK All Party Parliamentary Thrombosis Group. PE defined as I26.0 and I26.9. DVT defined as I80.1, I80.2, I80.3, I80.9 and I82.9
Germini 2016 [59]	Prospective cohort (quasi RCT) Intervention: Those admitted to Internal Medicine section 1 allocated to Padua prediction score decision strategy. Comparison: Those admitted to Internal Medicine section 2 allocated to clinical judgment-based strategy.	n = 628 All hospitalised acutely ill medical patients admitted into one of two Internal Medicine sections at the University Hospital in Perugia. Age: Range of medians 72-75 years Gender (male to female ratio): 340/288 Italy	DVT: defined with complete compression ultrasonography. PE: defined with CT angiography or V/Q lung scanning Fatal PE All-cause mortality Major bleeding: not defined.

Table 39: **Summary of studies included in the review: studies comparing achievement of >90% of admissions assessed using risk tool with <90%**

Study	Intervention and comparison	Population	Outcomes
Lester 2013 [102]	Retrospective cohort study Intervention: Use of Department of Health risk tool from July 2010 in achieving <90% VTE risk assessment Comparison:	n=17,712,681 All people admitted to 163 NHS hospitals in England (including general medical and surgical patients). Age: Not reported	VTE-related mortality post-discharge (90 days): death anywhere within the first three positions where VTE is considered either the direct cause or a contributing cause of death. Primary VTE-related mortality post-discharge (90

Study	Intervention and comparison	Population	Outcomes
	Use of Department of Health risk tool in March 2012 in achieving ≥90% VTE risk assessment	Gender (male to female ratio): Not reported UK	days): VTE code was listed in the first position of the death certificate, thus was considered the direct cause of death. VTE: defined using 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
Roberts 2013 [162]	Before and after study Before: Department of Health risk tool (April 2010-March 2011). After: Department of Health risk tool (April 2011-March 2012) use 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.	n=302,057 All patients admitted to one hospital. Age: Not reported Gender (male to female ratio): Not reported UK	VTE (90 days): 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. Identified 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 PE (90 days): definition not reported. DVT (90 days): definition not reported.

5.4.3   General medical points

5.4.3.1   Department of Health risk tool versus no risk tool

Table 40:   Clinical evidence summary: Department of Health risk tool versus no risk tool for general medical patients

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Department of Health risk tool	Risk difference with Department of Health risk tool (95% CI)
Mortality, VTE-related	100000 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	Rate ratio 0.92 (0.39 to 2.15)	0 per 1000 [c]	0 fewer per 1000 [c] (from 0 fewer to 0 more)
Readmission, VTE-related	100000 (1 study) 30 days	VERY LOW[a] due to risk of bias	Rate ratio 0.99 (0.82 to 1.19)	1 per 1000 [c]	0 fewer per 1000 [c] (from 0 fewer to 0 more)
Readmission, VTE-related	100000 (1 study) 90 days	VERY LOW[a] due to risk of bias	Rate ratio 1.02 (0.88 to 1.19)	2 per 1000 [c]	0 fewer per 1000 [c] (from 0 fewer to 0 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

c – Anticipated absolute effects could not be calculated accurately as only rate ratio was reported

5.4.3.2 **Department of Health risk tool: achieving >90% of admissions assessed using Department of Health risk tool versus achieving <90% assessed using risk tool**

Table 41: **Clinical evidence summary: Department of Health risk tool: achieving >90% of admissions assessed using Department of Health risk tool versus achieving <90% assessed using risk tool for general medical patients**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Department of Health risk tool	Risk difference with Department of Health risk tool (95% CI)
Mortality, VTE-related post-discharge – length of stay >3 days	2 590 547 (1 study) 90 days	VERY LOW[a] due to risk of bias	RR 0.96 (0.81 to 1.14)	-	- [c]
Mortality, VTE-related post-discharge - length of stay <4 days	10 719 502 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.74 (0.6 to 0.92)	-	- [c]
Mortality, primary VTE-related post-discharge - length of stay >3 days	2 590 547 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.89 (0.71 to 1.1)	-	- [c]
Mortality, primary VTE-related post-discharge - length of stay <4 days	10 719 502 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.62 (0.47 to 0.81)	-	- [c]
DVT	302057 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.95 (0.83 to 1.09)	3 per 1000	0 fewer per 1000 (from 0 fewer to 0 fewer)
PE	302057 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.79 (0.67 to 0.94)	11 per 1000	2 fewer per 1000 (from 1 fewer to 4 fewer)
VTE	302057 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.88 (0.79 to 0.98)	1 per 1000	0 fewer per 1000 (from 0 fewer to 0 fewer)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Department of Health risk tool	Risk difference with Department of Health risk tool (95% CI)
c - Could not be calculated as control group risk was not reported appropriately					

5.4.3.3 Padua prediction score versus no risk tool

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Padua prediction score versus no risk tool (95% CI)
DVT	628 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.55 (0.34 to 0.88)	155 per 1000	70 fewer per 1000 (from 19 fewer to 102 fewer)
PE	628 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 14.47 (0.25 to 830.93)	0 per 1000	- c
Fatal PE	628 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 14.47 (0.25 to 830.93)	0 per 1000	- c
Major bleeding	628 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	OR 0.2 (0.01 to 3.55)	5 per 1000	4 fewer per 1000 (from 5 fewer to 13 more)
All cause mortality	628 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.11 (0.32 to 3.91)	15 per 1000	2 more per 1000 (from 10 fewer to 44 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Padua prediction score versus no risk tool (95% CI)
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.					
c Absolute effects could not be calculated due to zero events in control arm					

5.4.4 Surgical patients

5.4.4.1 Caprini risk tool versus no risk tool

Table 42: Caprini risk tool versus no risk tool for surgical patients

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Caprini risk tool	Risk difference with Caprini risk tool (95% CI)
DVT	2892 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, indirectness,	RR 0.11 (0.04 to 0.32)	23 per 1000	20 fewer per 1000 (from 15 fewer to 22 fewer)
PE	2892 (1 study) 30 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.49 (0.2 to 1.17)	11 per 1000	6 fewer per 1000 (from 9 fewer to 2 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment as the study was conducted in the USA, there are differences in clinical practice
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

5.4.4.2 **Department of Health risk tool: achieving >90% of admissions assessed using Department of Health risk tool versus achieving <90% assessed using risk tool**

Table 43: **Department of Health risk tool: achieving >90% of admissions assessed using Department of Health risk tool versus achieving <90% using risk tool for surgical patients**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Department of Health risk tool	Risk difference with Department of Health risk tool (95% CI)
Mortality, VTE-related post-discharge - length of stay >3 days	1 550 794 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.73 (0.46 to 1.16)	-	- c
Mortality, VTE-related post-discharge- length of stay <4 days	2 851 838 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.82 (0.65 to 1.03)	-	- c
Mortality, primary VTE-related post-discharge- length of stay >3 days	1 550 794 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.62 (0.44 to 0.89)	-	- c
Mortality, primary VTE-related post-discharge - length of stay <4 days	2 851 838 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.57 (0.3 to 1.06)	-	- c

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

c - Could not be calculated as control group risk was not reported appropriately

5.4.5   Economic evidence

Published literature

Two health economic studies were identified with the relevant comparisons and have been included in this review.[99, 115] These are summarised in the health economic evidence profiles below (Table 44 and Table 45) and the health economic evidence table in appendix J.

See also the health economic study selection flow chart in appendix F.

New economic analysis

A cost impact analysis was also undertaken to aid the committee's decision making. In this analysis, with support from committee members, the speciality codes for general medical patients were identified. Using NHS Digital, Hospital Episode Statistics (HES) for 2015/16, the number of bed days for people who stayed in hospital as general medical patients for more than 3 days was identified (18.8 million).

The committee members advised that the National risk assessment tool used currently results in 80% of people having pharmacological prophylaxis. It is anticipated that the IMPROVE risk assessment tool would result in around 40% of people having prophylaxis; in line with the intermediate eligibility group in the Miller study.[115]   The cost of prophylaxis per bed day is £3.03. The difference in the number of bed days at 80% and 40% prophylaxis was multiplied by the cost per day. This was then adjusted for an increase in costs due to increased cases of DVT and PE using Millar 2016. [115] The net saving from this reduction in prophylaxis is estimated to be around £22.3 million.

Table 44:   Health economic evidence profile: Risk assessment tools vs no risk assessment tool

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Lecumberri 2011[99] [Spain]	Partially applicable [(a)]	Potentially serious limitations[(b)]	**-Population:** All hospitalised adult inpatients (medical and surgical) at the University Clinic of Navarra. The population also included pregnant women but very small percentage ranging between 3.2 to 4.4% across the follow-up periods. **-Study design:** cost-consequences analysis based on a before-and-after cohort study. **-Interventions:** **Intervention 1:** No e-alert system to stratify patients' risk of thrombosis. **Intervention 2:** E-alert software to identify hospitalised patients at risk of VTE. The risk assessment scoring systems used were: PRETEMED scale (a validated risk stratification tool) for medical patients) and ACCP guidelines for surgical patients.	2 vs 1 Saves £6 per patient	2 vs 1: **VTE events:** 1 to 2 fewer VTE events per 1000 patients **Major bleeding:** 10 fewer major bleeding events per 1000 patients	Using risk assessment tools is dominant	None of the sensitivity analyses results in a change of the conclusion regarding dominance of the intervention.

Abbreviations: VTE: venous thromboembolism

(a) The risk assessment tools used are different from those included in the clinical review. QALYs are not used as measure of outcome. Uncertainty regarding the applicability of costs and resource use from the Spanish health care system in 2011 to current NHS perspective.

(b) The economic analysis is conducted alongside a single observational study, so by definition does not reflect all evidence in this area. Short follow-up period, so long terms and consequences have not been included. Unit costs are based on local rather than national sources; hence it is not clear if these are generalisable.

Table 45:   Health economic evidence profile: prophylaxis based on risk stratification using individual risk factors vs no prophylaxis

Study	Applicability	Limitations	Other comments	Cost	Effects	Incremental costs	Incremental effects	Cost effectiveness	Uncertainty
Millar 2016 [115] ([Australia])	Partially applicable[(a)]	Potentially serious limitations [(b)]	• **Study design:** Cost consequences analysis using Decision tree model based on the results of a single RCT (the PREVENT trial) • **Population**: adult internal medicine patients admitted to all Australian hospitals • **Interventions:** 1. No prophylaxis 2. VTE prophylaxis using LMWH (Enoxaparin 40 mg/day). Three levels of eligibility for prophylaxis were examined: 2.a. restricted[(d)] (25% of all admissions), 2.b. intermediate[(c)] (40% of all admissions) and 2.c. broad[(e)] (80% of all admissions)	1. £29 2.a. £26 2.b. £30 2.c. £39	1. 4.3 DVTs, 2.3 PEs, 0.4 deaths per 1000 2.a. 2.5 DVTs, 2 PEs, 0.5 deaths per 1000 2.b. 2.4 DVTs, 1.99 PE, 0.6 deaths 2.c. 2.1 DVTs, 1.93 PEs, 0.9 deaths per 1000	DVT: No prophylaxis: dominated Restricted eligibility: baseline Intermediate eligibility: extendedly dominated Broad eligibility: £29,861 per DVT averted PE: No prophylaxis: dominated Restricted eligibility: baseline Intermediate eligibility: extendedly dominated Broad eligibility: £170,827 per PE averted Deaths: No prophylaxis: £30,000 per death averted Restricted eligibility: baseline Intermediate eligibility: dominated Broad eligibility: dominated			A range of sensitivity analyses were conducted including changing baseline VTE risk, fatality rate for PE and major bleeding and assumptions regarding VTE risk in non-eligible patients.

Abbreviations: DVT: deep vein thrombosis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; PE: pulmonary embolism; QALY: quality-adjusted life years; RCT: randomised controlled trial; VTE: venous thromboembolism.

(a) Some uncertainty regarding the applicability of resource use and cost data from Australia in 2014 to current NHS context. Discounting was used only for health outcomes and the rate used is different from that recommended in the NICE Reference Case. QALYs are not used as an outcome measure.

(b) *The model has a short time horizon that covers only the duration of the hospital stay, hence, does not capture long term costs. Only symptomatic events are included in the model. The source of baseline risk and relative treatment effects is based on a single trial and is not reflective of the total body of evidence. The results of the costs and outcomes are not presented as means per patient.*

(c) *Restricted: where only patients with strongest risk factors were given prophylaxis (malignancy, especially with chemotherapy, previous history of VTE, some rarer high risk conditions such as inflammatory bowel disease. (~ 25% of all inpatient admissions)*

(d) *Intermediate: where patients with strong and moderate risk factors, such as cardiac or respiratory failure, sepsis or inflammation, are given prophylaxis (~ 40% of all inpatient admissions)*

(e) *Broad: where everyone from the intermediate group as well as those satisfying an age criterion (>40 or >60) are given prophylaxis (~80% of all inpatient admissions)*

5.4.6 Evidence statements

Clinical

For assessing VTE risk in general medical patients, very low quality evidence from one large study (n=100,000) showed no clinical difference in mortality, or 30 and 90 day readmission rates when the Department of Health risk tool was used compared to no risk tool being used. When the quality standard of assessment of 90% of admissions with the Department of Health risk tool had been achieved, very low quality evidence from another large study (n=10,719,502) suggested a clinical benefit for possible VTE-related, and primary VTE-related, mortality post-discharge following a hospital stay of less than 4 days. However the uncertainty around these effects means the estimates could also be consistent with no difference. No clinical difference was found between the ≥90% and <90% DOH assessed groups for the same mortality outcomes in patients whose hospital stay was longer than 3 days, and for VTE, DVT and PE. When general medical patients were risk assessed with the Padua prediction score, very low quality evidence from one study (n=628) suggested a possible clinical benefit for all-cause mortality, DVT and major bleeding, compared to those assessed with clinical-judgment only (no risk tool), although there was large uncertainty around all these estimates.

For assessing VTE risk in surgical patients, very low quality evidence from one study (n=2892) showed a clinically important reduction in DVT when assessing surgical patients with the Caprini risk tool compared to no risk tool. Very low quality evidence from the same study also suggested a lower PE rate in those assessed with the Caprini risk tool; however uncertainty around the PE estimate is also consistent with no difference. When the quality standard of assessment of 90% of admissions with the Department of Health risk tool had been achieved, very low quality evidence from another large study (n=1,550,794) suggested a clinical benefit for possible VTE-related, and primary VTE-related, mortality post-discharge following a hospital stay of more than 3 days, and primary VTE-related, mortality post-discharge following a hospital stay of less than 4 days. However the uncertainty around these effects means the estimates could also be consistent with no difference.

Economic

- One cost-effectiveness analysis found that in people admitted to hospital risk assessment using PRETEMED scale (a validated risk stratification tool) for medical patients and ACCP guidelines for surgical patients was dominant (less costly and more effective) compared to no risk assessment. This study was assessed as partially applicable with potentially serious limitations.

- One cost-consequences analysis found that in adults admitted to internal medicine department restricting eligibility for prophylaxis to the top 25% based on risk assessment using individual risk factors was dominant (less costly and more effective) compared to no prophylaxis. This study was assessed as partially applicable with potentially serious limitations.

5.5 Risk assessment for people having day procedures

Accuracy of risk assessment tools for VTE for day procedures

5.5.1 Review question: 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?

For full details see review protocol in appendix C.

Table 46: PICO characteristics of review question

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?
Population	Adults and young people (aged 16 or over) who are having day procedures (including surgery and chemotherapy)
Risk tool	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) • VTE-related mortality (7- 90 days; up to 180 days for people having cancer treatment) • DVT alone (7- 90 days; up to 180 days for people having cancer treatment) • PE alone (7- 90 days; up to 180 days for people having cancer treatment)
Outcomes (in terms of predictive test accuracy, calibration)	Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values) • 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 Exclusions: derivation studies

5.5.2   Clinical evidence

Seven studies evaluating 2 risk tools were included in the review, [9, 17, 27, 91, 148, 186, 193] these are summarised in Table 47 below. See also the study selection flow chart in appendix E, study evidence tables in appendix H, and excluded studies list in appendix N. Full details of the tools included in this review are provided in the clinical evidence tables in appendix H.

Five of the papers explored the predictive ability of the Khorana Score in a range of cancer patients, one explored an unnamed risk tool for cancer patients and the seventh paper explored an unnamed risk tool for surgical outpatients.

Table 47: Summary of studies included in the review

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
People undergoing cancer treatment					
Ay 2010[9]	Khorana score	n=819 People with cancer undergoing chemotherapy, radiotherapy and/or surgery Primary site of cancer: Breast 17.1% Lung 15.3% Stomach 4.4% Colorectal 13.7%	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	n= 61 (7.4%)	Prospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		Pancreas 5.7% Kidney 2.9% Prostate 13.7% Brain (high-grade glioma) 13.1% Lymphoma 11.8% Multiple myeloma 2.2% Austria	tomography or ventilation/perfusion lung scan for diagnosis of pulmonary embolism (PE) Sensitivity Specificity NPV PPV		
Bezan 2017 [17]	Unnamed risk stratification model	n=349 People with testicular germ cell tumours Seminoma 56.8% Non-seminoma 43.2% Stage IA-B 64.8% Stage IS 2.6% Stage II1-IIC 14.3% Stage IIIA-C 18.3% Switzerland	VTE (12 months): not defined C-statistic	n=18 (5.2%)	Retrospective cohort
Cella 2017 [27]	Khorana score	n=843 People with active cancer undergoing chemotherapy, endocrine therapy, radiotherapy, target therapy and/or surgery in combination or alone. Primary tumour site: Breast 37% Gastroenteropancreatic 30% Genito/urinary tract 13% Lung 4% Metastatic disease 55% Other 16.5% Italy and Germany	VTE (12 months)L defined by Doppler ultrasound and CT Sensitivity Specificity C-statistic	n=73 (8.6%)	Retrospective cohort
Khorana 2008 [91]	Khorana score	n=1365 People with cancer undergoing chemotherapy	VTE (timepoint unclear): not defined Sensitivity Specificity	n=28 (2.1%)	Prospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		Primary site of cancer: Breast 34.6% Lung 17.3% Lymphoma 13.5% Colorectal 11.9% Gynaecologic 10.40% Gastric and pancreatic 1.4% Age: <65 years 62.3%; ≥65 years 37.7% Gender (male to female ratio): 1:2 USA	NPV PPV C-statistic Hosmer-Lemeshow test		
van Es 2017 [186]	Khorana Score	n=876 Ambulatory cancer patients with solid tumours Age, mean (SD): 64 (11) years 56% male Tumour type Lung 26% Oesophagus 19% Colorectal 18% Pancreas 12% Breast 9% Prostate 5% Gastric 5% Ovarian 5% Bladder 1% The Netherlands, Italy, France and Mexico	VTE (6 months): objectively confirmed symptomatic PE and DVT C-statistic	n=53 (6.1%)	Prospective cohort
Wang 2017 [193]	Khorana Score	n=270 People with hepatocellular carcinoma (HCC) Age, mean (range): 58.5 (26-80)	VTE (time point not defined) based on radiographic examinations using compression ultrasound, contrast-enhanced CT, and pulmonary angiogram	n=16 (5.93%)	Retrospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		Gender (M/F): 50/220

HCC with Barcelona stage 0-A 42.6%
Advanced HCC with Barcelona stage C or D 57.4%

USA | Sensitivity
Specificity | | |
| **People undergoing surgery** | | | | | |
| Pannucci 2012[148] | Unnamed (Pannucci 2012) | n=85,730

Surgical outpatients

Herniorrphaphy:33%
Integument: 22%
Liver, biliary system, and pancreas: 13%
Musculoskeletal: 9.1%
Arteries and veins: 6.4%
Hindgut (small bowel, large bowel, rectum and anus): 4.7%
Endocrine: 3%
Genital system (male or female): 2%
Foregut (stomach, including gastric bypass procedure): 1.6%
Head and neck, oesophagus: 1.5%
Urinary system: 1.2%
Hemic and lymphatic system, mediastinum and diaphragm: 0.9%
Miscellaneous peritoneal procedures: 0.9%
Nervous system structures: 0.5%
Respiratory and cardiovascular: 0.1%

Age (derivation and validation cohort): < 40 years 18.5%; 40-59 years 45.5%; 60 years 36%

Gender (male to female ratio) (derivation and | 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)

C-statistic
Hosmer-Lemeshow test | DVT: n=87 (0.10%)

PE: n=37 (0.043%) | Prospective cohort |

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		validation cohort): 1:1.4 USA			

5.5.3 Discrimination

5.5.3.1 People undergoing surgery

Table 48: Clinical evidence profile: risk tools for predicting VTE in people undergoing surgical day procedures

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Unnamed (Pannucci 2012)	1	85,730	Serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	-	-	0.78 (0.72 - 0.84)	MODERATE

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making.

(a) *Risk of bias was assessed using the PROBAST checklist items relating to risk of bias*

(b) *Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).*

(c) *Indirectness was assessed using the PROBAST checklist items relating to applicability*

(d) *Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20%-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.*

5.5.3.2 People having cancer treatment

Table 49: Clinical evidence profile: risk tools for predicting VTE in people having cancer day treatment

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic median (range)	Quality
Khorana Score										

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic median (range)	Quality
Khorana score (≥3) *Pooled estimate*	5	4173	Very serious risk of bias[a]	Serious inconsistency[b]	No serious indirectness[c]	Very serious imprecision[d]	15.99% (1-55)	95.80% (82-99)	0.583 (0.47-0.70)	VERY LOW
Unnamed tools										
Unnamed risk stratification model (Bezan 2017)	1	349	Very serious risk of bias[a]	No serious inconsistency[b]	Very serious indirectness[c]	Not estimable	-	-	0.84	LOW

The assessment of the evidence quality was conducted with emphasis on test specificity as this was the primary measure discussed in decision making.

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias

(b) Inconsistency was assessed by inspection of the sensitivity/specificity (based on the primary measure) forest plots, or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which would be acceptable to recommend a test). For example, the committee might set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by one increment if the individual studies varied across two areas (eg. 50-90% and 90-100%) and by two increments if the individual studies varied across three areas (eg. 0-50%, 50-90% and 90-100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability

(d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

5.5.4 Calibration

5.5.4.1 People undergoing surgery

Table 50: Clinical evidence profile: risk tools for predicting VTE in people undergoing surgical day procedures

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R^2 (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
Unnamed (Pannucci 2012)	1	85,730	Serious risk of bias[a]	No serious indirectness[b]	Not estimable	-	0.826	-	-	MODERATE

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making.
(a) Risk of bias was assessed using the PROBAST checklist.
(b) Indirectness was assessed using the PROBAST checklist items relating to applicability

5.5.4.2 People having cancer treatment

5.5.5 People having cancer treatment

Table 51: Clinical evidence profile: risk tools for predicting VTE in people having cancer day treatment

Risk tool	No of studies	n	Risk of bias	Indirectness	Imprecision	R^2 (95%CI)	Hosmer-Lemeshow test (p-value)	Brier score (95%CI)	D statistic	Quality
Khorana score Khorana 2008	1	1365	Serious risk of bias[a]	Serious indirectness[b]	Not estimable	-	0.15	-	-	LOW

The assessment of the evidence quality was conducted with emphasis on test specificity as this was the primary measure discussed in decision making.
(a) Risk of bias was assessed using the PROBAST checklist.
(b) Indirectness was assessed using the PROBAST checklist items relating to applicability

5.5.6 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the economic article selection flow chart in appendix F.

5.5.7 Evidence statements

Clinical

Moderate quality evidence from a single study (n=85,730) suggested moderate discrimination for an unnamed tool at predicting risk of VTE for people undergoing surgical day procedures with calibration data of 0.826. No further discrimination data was reported.

Very low quality evidence from a diagnostic meta-analysis of 5 papers (n=4173) showed sensitivity of 15.99% (1-55) and specificity of 95.80% (82-99) for the Khorana Score at predicting VTE based on a high-risk cut-off of ≥3. There was very serious uncertainty around the estimate for sensitivity. This sensitivity was far below the pre-specified threshold set by the committee. Three of the five papers presented c-statistics which ranged from 0.47 to 0.70 with a median poor discrimination of 0.583.

Economic

No relevant economic evaluations were identified.

5.6 Accuracy of risk assessment tools for bleeding for day procedures

5.6.1 Review question: 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 having day procedures (including surgery and chemotherapy) at hospital?

For full details see review protocol in appendix C.

Table 52: PICO characteristics of review question

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?
Population	Adults (aged 16 or over) who are having day procedures (including surgery and chemotherapy)
Risk tool	Derived and (externally or temporally) validated risk tools identified in literature
Target condition(s)	Major bleeding (up to 90 days)
Outcomes (in terms of predictive test accuracy, calibration)	Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values) • 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 Exclusions: derivation studies

5.6.2 Clinical evidence

No studies evaluating risk tools for predicting major bleeding associated with VTE in people having day procedures were included in the review. See the study selection flow chart in appendix E, study evidence tables in appendix H, and excluded studies list in appendix N. Full details of the tools included in this review are provided in the clinical evidence tables in appendix H.

5.6.3 Discrimination

No relevant studies were identified.

5.6.4 Calibration

No relevant studies were identified.

5.6.5 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

5.6.6 Evidence statements

Clinical

No relevant studies were identified.

Economic

No relevant economic evaluations were identified.

5.7 Effectiveness of risk assessment tools for day procedures

5.7.1 Review question: How clinically and cost effective are risk assessment tools at reducing the rate of VTE in patients who are having day procedures (including surgery and chemotherapy) at hospital?

For full details see review protocol in appendix C.

Table 53: PICO characteristics of review question

Population	Adults (aged 16 or over) who are having day procedures (including surgery and chemotherapy)
Intervention(s)	Derived and validated risk tool for predicting the risk of VTE/DVT/PE/major bleeding The Department of Health risk tool (not validated)
Comparison(s)	No risk tool, other risk tools
Outcomes	Critical: • All-cause mortality (up to 90 days from hospital discharge) • VTE (symptomatic or asymptomatic) (up to 90 days from hospital discharge) • DVT (symptomatic or asymptomatic) (up to 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) • 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)

5.7.2   Clinical evidence

No relevant clinical studies were identified that compared validated risk tools with other or no risk tools, which predicted the risk of VTE, DVT, PE or major bleeding in people having day procedures. See the study selection flow chart in appendix E and excluded studies list in appendix N.

5.7.3   Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

5.7.4   Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

No relevant economic evaluations were identified.

5.8   Recommendations and link to evidence

Recommendations	Risk assessment **1.1.1 Assess all patients to identify the risk of venous thromboembolism (VTE) and bleeding (see recommendations 1.1.2, 1.1.5, 1.1.9, 1.4.17 and 1.4.23)** **People admitted to hospital**

	Medical patients **1.1.2 Assess all medical patients to identify the risk of VTE and bleeding:** • **as soon as possible after admission to hospital or by the time of the first consultant review** • **using a tool published by a national UK body, professional network or peer-reviewed journal. The most commonly used risk assessment tool for medical patients is the Department of Health VTE risk assessment tool[mmm] (See Appendix T) . [2018]** **1.1.3 Balance the person's individual risk of VTE against their risk of bleeding when deciding whether to offer pharmacological thromboprophylaxis to medical patients. [2018]** **1.1.4 If using pharmacological VTE prophylaxis for medical patients, start it as soon as possible and within 14 hours of admission, unless otherwise stated in the population-specific recommendations (see chapters 9-13). [2018]**
Research recommendation	**1. What is the accuracy of individual risk assessment tools in predicting the risk of VTE and risk of bleeding in medical patients admitted to hospital?**
Relative values of different outcomes	Predictive accuracy of VTE and bleeding risk tools The committee was interested in the prognostic accuracy of risk assessment tools for medical patients admitted to hospital or who are in hospital having day procedures. A risk assessment tool would be used to identify people with an increased risk of VTE who would benefit from having VTE prophylaxis, or identify people with an increased risk of major bleeding in order to determine appropriate prophylaxis strategies, for example not giving pharmacological prophylaxis to people who are at a high risk of bleeding. The committee agreed that sensitivity was more important than specificity in medical patients because people who are at higher risk of VTE could be identified for potential VTE prophylaxis treatment (fewer false negatives). The committee set thresholds for the acceptability of a test; for the populations noted here, these were ≥80% sensitivity and ≥60% specificity. Some studies only reported a C-statistic. The committee acknowledged that this metric was important for comparing the overall accuracy of the tools, but in itself was unlikely to provide enough information on which to base a recommendation as it does not indicate the number of false positives and negatives of the tool. Therefore, the committee decided against recommending a tool without sensitivity and specificity data. Clinical effectiveness of risk tools for reducing VTE For the review of the clinical effectiveness of risk tools, the committee considered all-cause mortality, VTE (symptomatic or asymptomatic), DVT (symptomatic or asymptomatic), PE, fatal PE, major bleeding and quality of life as critical outcomes. The time points for these outcomes were up to 90 days from hospital discharge. The committee considered fatal bleeding, clinically relevant non-major bleeding, heparin-induced thrombocytopenia, hospital length of stay, unplanned readmission and haemorrhagic stroke as important outcomes. The time points for these outcomes were up to 90 days, apart from clinically relevant non-major bleeding up to 45 days

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	from hospital discharge. Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	Predictive accuracy of VTE and bleeding risk tools
Fourteen studies were identified looking at risk tools for predicting VTE in medical patients. Eight papers featured people admitted to hospital and six featured those having day procedures, all of whom were people coming into hospital to receive cancer treatment. One study was identified looking at a risk tool to predict the risk of major bleeding in hospitalised medical patients. PROBAST was used to assess the risk of bias. All these studies were at a high or very high risk of bias. Common reasons for this were papers only supplying retrospective validation, papers not reporting a clear definition or method of confirmation for the target condition (VTE, DVT, PE or major bleeding), papers not reporting the time-point for the target condition measurement, or unclear flow and timing between when the risk score was calculated and when the outcome was measured. There were also very low event rates in many of the studies and therefore not a reasonable number of outcome events compared to the number of factors in the risk tool. Many papers also failed to report all the relevant performance measures (sensitivity and specificity).
The committee were concerned about the applicability of some risk tools for UK practice due to the setting the tool was originally derived in as well as the location of the validation studies. The committee noted the differences in care settings and medical practices in the US and decided to downgrade any papers from a US setting for indirectness (see further detailed discussion on this in the following section).
Clinical effectiveness of risk tools for reducing VTE
No randomised controlled trials were identified, therefore observational studies were considered for inclusion in this review. Four observational studies were included in this review (one retrospective cohort study and three before-and-after studies). Two of the studies compared use of a risk tool versus with no risk tool (the National VTE Risk Assessment Tool [otherwise known as the Department of Health tool, please see the other considerations section for further detail] and the Padua Prediction Score); and two studies compared achieving the quality standard of 90% of admissions being assessed with the National VTE Risk Assessment Tool with not achieving the quality standard.
The committee discussed the need for caution when evaluating evidence from quality standard cohort papers and before-and-after studies due to the risk of bias inherent in these designs. The four observational studies provided evidence of very low quality due to risk of bias, primarily based on selection bias and incomplete outcome data; and imprecision around the effect estimates.
Trade-off between clinical benefits and harms	There is no established definition of medical patients, and the papers included in this review cover different groups of people including acutely ill medical patients, people who have had acute stroke and people with cancer; all with different associated thrombotic and bleeding risks. The rate of VTE identified in the evidence ranged from 0.5-4.5%. This large disparity is due to a number of factors, including: the heterogeneous group of patients; different study designs including RCT, prospective and retrospective cohorts and database/registry studies; and different definitions of the VTE endpoint (asymptomatic or symptomatic). Of the 18 studies reporting on risk tools in medical patients only three of these were undertaken in the UK NHS context. All three of these looked only at the National VTE Risk Assessment Tool (hereafter referred to as the National Tool) but none were designed specifically to validate whether this tool can adequately predict risk of VTE or risk of bleeding the UK population.
Evidence was identified for a number of VTE risk assessment tools for medical patients including the Padua prediction score, the Kucher score, the Intermountain score and the IMPROVE tool. Evidence was also identified for a bleeding risk version of the IMPROVE tool. The committee discussed these tools at length including the

various risk factors that went into them and whether these were weighted or not. The committee noted that the National Tool and Intermountain score performed more like a checklist as they are not weighted tools but instead involve an in-or-out decision. The committee determined that none of the tools demonstrated sufficiently accurate performance for predicting VTE or bleeding risk based on the evidence, with none reaching the committee's pre-specified sensitivity and specificity thresholds and many reporting only poor discrimination.

All committee members agreed that risk assessment is a critical part of the pathway for VTE prophylaxis. They also agreed that risk tools are beneficial in this process. However, in the absence of clear evidence there was disagreement about which tool to recommend. Based on its increasing use in the US context, initial discussions considered whether the IMPROVE Tool should be recommended over current practice, which is the National Tool.

There are two different versions of the IMPROVE tool. The 4-factor version of the tool is known as the predictive version because information on all 4 factors the tool measures should be available at admission and are considered to be predictive of VTE during the 3-month period following hospital admission.[179] The 7-factor version of the tool is known as the association version because some of the extra factors will require judgement of in-hospital factors that cannot be known for certain on admission (for example expected number of days the person might be immobilised) that are believed to be associated with an increased risk of VTE during the 3-month period following hospital admission.[179] Evidence included in this review is for the 4-factor version of IMPROVE as this was the only version with an identified validation study that met the inclusion criteria for the review. No validation studies of the 7-factor tool met the criteria in the review protocol.

The committee noted that the National Tool has been embedded in practice for 7 years with a high level of adherence. However, several committee members were of the opinion that the tool leads to over prescribing of prophylaxis in medical patients without clear evidence of benefit, potentially incurring a significant cost to the NHS. Around 73% of medical patients in the UK receive prophylaxis using the National Tool (NHS Safety Thermometer Data – March 2016 to March 2017, published April 12, 2017; accessed 15 August 2017) compared to around 40% of medical patients (in largely US based populations) for other tools. [64] The committee considered the high rate of prophylaxis being given was in part due to the way the National Tool is being used in practice. The National Tool may have become a 'tick-box exercise' where clinicians view it as a unweighted checklist of risk factors; if you tick one box (a single risk factor), that equates to a high VTE risk and this automatically results in prophylaxis being offered. The committee stressed that this has led to a larger number of medical patients receiving VTE prophylaxis than would be expected. Most importantly this fails to highlight the clinical judgement that must come into play in order to consider whether individual risk factors lead to an overall increased risk, and the balance of this with any bleeding risk factors or other contraindications. The committee understood that none of the identified tools, nor the currently practiced National Tool, offer clear guidance on how to balance VTE risk and bleeding risk to come to a decision on whether to offer prophylaxis, and if so what type. While the IMPROVE tool has both a VTE risk and bleeding risk version, both of which are available in online calculator format (beta version and no validation available), these also only provide a percentage risk for each outcome with no guidance on how to balance the two.

The committee also discussed the indirect context of the evidence for the IMPROVE tools (both the VTE risk version and the bleeding risk version). In particular the committee highlighted that in the US a much higher proportion of medical patients are cared for on intensive care wards (ICU), whereas in the UK it is only the very ill (generally those in need of artificial ventilation) who are moved to critical care – so the baseline condition of the two populations would be very different. The 7-factor version of the IMPROVE tool has ICU/CCU stay as a major risk component and this would contribute to different risk assessment interpretations in the UK compared to

the US population in which the tool is validated. The committee also acknowledged that the average length of stay in intensive care is around 7 days in the USA, compared to a shorter stay of approximately 2–3 days in the UK. This is reflected in the National Tool listing mobility significantly reduced ≥3 days as a risk, and the 7-factor IMPROVE tool listing immobilisation ≥7 days as a risk. Factors such as these require the clinician to make judgements about anticipated patient features that cannot be known with certainty at admission. The committee pointed out that tools that require information that may not be available at the point of admission are not practical.

Overall, the committee agreed that there is a lack of good quality evidence for any tool. The following options were considered as recommendations for assessing risk in medical patients:

(1) use the National Tool

(2) use the IMPROVE Tool

(3) use either the National Tool or the IMPROVE Tool

(4) consider medical patients at risk if immobility was a factor and they have an additional risk factor, with individual risk factors being provided as examples in a box;

(5) use an existing derived or validated tool or checklist.

After considerable debate a committee meeting consensus was reached to rule out the first 3 options. However, no consensus was reached on whether to recommend options number 4 or 5. The main arguments behind supporting each of these options were:

- Those favouring option 4 expressed concerns with recommending option 5. They were concerned about organisational rigour in a resource-stretched NHS and that the decision on which tool to use will be made that may not be in the patient's best interest. A particular tool may be chosen because of potential cost saving benefit and not because it is considered to be more accurate or effective.

- Those favouring option 5 believed it better reflects the uncertainty in evidence as there is no clear evidence that one tool is better than another. It allows clinicians to decide which tool to use whereas option 4 seemed too similar to current practice. It would also prompt clinicians to consider that risk assessment for VTE is not just a checklist of risk factors that once ticked automatically mean prophylaxis, it is a balance between VTE risk and bleeding risk which requires clinical judgement before the decision to offer prophylaxis is made.

Because of the split decision the committee voted for one of these two options and agreed whichever option had the most votes would determine the recommendation. The vote produced a majority favouring option 5. Following stakeholder consultation the committee also decided to acknowledge in the recommendation that the most commonly used VTE risk assessment tool for hospital patients in the NHS is the National Tool (see appendix T).

Reflecting the uncertainty in the evidence for one risk tool over another, the committee prioritised a research recommendation in this area.

Trade-off between net clinical effects and costs	Two economic studies were included. One of the studies compared the use of a risk assessment tool for medical patients based on the PRETEMED scale (a validated risk stratification tool for medical patients) which was integrated in the hospital electronic system in the form of an e-alert system. The second study assessed the impact of restricting the provision of LMWH prophylaxis based on a list of risk factors that allow restricted, intermediate or broad eligibility for prophylaxis in general medical patients admitted to hospital. The committee discussed the two studies and noted that the study that compared using a risk assessment tool to not using one showed that the use of a risk assessment tool was dominant (both more effective

and less costly). The committee acknowledged however that the tool used in this study was not validated and was not one of those identified in the clinical review.

The committee highlighted that all the risk tools included in the clinical review are generally not associated with any licencing cost although some may require a specific software installation. However, the committee acknowledged that the prognostic performance of the risk tool, as well as the baseline risk in the target population, would determine the number of individuals who would receive prophylaxis. The choice of a tool that has high specificity would minimise the cost of unnecessary prophylaxis provision. If the specificity of a tool is low, there is a risk that a large number of people will be triggered for further care that they do not require (over-treatment), which would make the tool unlikely to be cost-effective. Conversely, if the tool has low sensitivity then a large number of people will not be identified as being at risk of VTE, and therefore not receive the prophylaxis they could benefit from. The committee determined that the evidence for the prognostic accuracy of the tools identified was inconclusive and does not support recommending one tool over another. This increases the uncertainty in the cost effectiveness of these tools.

The committee acknowledged that the use of the National Tool is considered current practice for surgical, medical and trauma patients. Hence, any changes are likely to have cost impact.

For medical admissions, the committee discussed the potential of using the IMPROVE tool, both the 4- and 7- factor versions; however there were concerns about the fact that neither has been validated in a UK population. Furthermore, the tool mainly assesses the risk of symptomatic VTE and does not identify patients at risk of developing an asymptomatic DVT.

A cost impact analysis was also undertaken to aid the committee's decision making. This analysis showed that using the IMPROVE risk assessment tool would result in around 40% of people having prophylaxis, in line with the intermediate eligibility group in the Miller study. The saving from this reduction in prophylaxis is estimated to be around £22.3 million.

However after the extensive discussions and voting process outlined above, it was determined that the evidence underpinning the accuracy and effectiveness of IMPROVE and all the tools considered for medical patients (including the National Tool) did not show that one tool is better than the other and a research recommendation was made to allow for future research to address the uncertainty in this area.

Other considerations	The National VTE Prevention Programme was launched in England in 2010 mandating VTE risk assessment in all adult patients admitted to an acute hospital, using a National VTE risk assessment tool.[161] The committee noted that CG92 and the National Tool were published concurrently in 2010, therefore CG92 did not recommend the National Tool by name. However, it was also noted that the recommendation in CG92 and the National Tool is identical.
	The initial goal as part of the Commissioning for Quality Innovation (CQuIN) Framework was to set a 90% target of all patients risk assessed for VTE. This was supported by a financial incentive (CQuIN) payment and within 3 years this goal was increased to 95% which has been exceeded in subsequent years.[161] However the committee noted that there have been no published studies examining the long-term impact of the National VTE prevention programme, specifically no research has been conducted validating the National Tool's performance at predicting medical patients' risk of VTE and risk of bleeding. The committee expressed their disappointment in this, especially as this was an area highlighted for further research by the CG92 committee.
	The committee made a high-priority research recommendation on risk assessment tools; see appendix R for more details.
	The committee discussed giving guidance on the appropriate time to initiate

pharmacological prophylaxis following completion of the risk assessment. In particular the committee wanted to highlight that, if using pharmacological prophylaxis, it should be given in a timely manner to ensure that people are not left for too long without it if they happened to be admitted shortly after what is usually a set daily time for doses to be given on a ward. The committee recommend a time point that is in line with current NHS policy on time to consultant review of acute inpatients. This standard states that all emergency admissions must be seen and have a thorough clinical assessment by a suitable consultant as soon as possible, but at the latest within 14 hours from the time of admission to hospital.[134] The committee agreed that recommending a similar timeframe within which pharmacological prophylaxis should be given (if indicated by risk assessment) makes logical clinical sense and will ensure clinical care is not delayed.

Recommendations	*Surgical and trauma patients*
	1.1.5 Assess all surgical and trauma patients to identify the risk of VTE and bleeding:
	• **as soon as possible after admission to hospital or by the time of the first consultant review**
	• **using a tool published by a national UK body, professional network or peer-reviewed journal. The most commonly used risk assessment tool for surgical patients is the Department of Health VTE risk assessment tool[nnn] (See Appendix T). [2018]**
	1.1.6 Balance the person's individual risk of VTE against their risk of bleeding when deciding whether to offer pharmacological thromboprophylaxis to surgical and trauma patients. [2018]
	1.1.7 If using pharmacological VTE prophylaxis for surgical and trauma patients, start it as soon as possible and within 14 hours of admission, unless otherwise stated in the population-specific recommendations (see chapters 9-13). [2018]
Research recommendation	**1. What is the accuracy of individual risk assessment tools in predicting the risk of VTE and risk of bleeding in surgical and trauma patients admitted to hospital?**
Relative values of different outcomes	**Predictive accuracy of VTE and bleeding risk tools**
	The committee was interested in the prognostic accuracy of risk assessment tools for surgical and trauma patients admitted to hospital or who are in hospital having day-case surgery. A risk assessment tool would be used to identify people with an increased risk of VTE who would benefit from having VTE prophylaxis, or identify people with an increased risk of major bleeding in order to determine appropriate prophylaxis strategies, for example not giving pharmacological prophylaxis to people who were at a high risk of bleeding.
	The committee agreed that sensitivity was more important than specificity in surgical patients because people who are at higher risk of VTE could be identified for potential VTE prophylaxis treatment (fewer false negatives). The committee set thresholds for the acceptability of a test; for the populations noted here, these were

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≥80% sensitivity and ≥60% specificity.

Some studies only reported a C-statistic. The committee acknowledged that this metric was important for comparing the overall accuracy of the tools, but in itself was unlikely to provide enough information on which to base a recommendation as it does not indicate the number of false positives and negatives of the tool. Therefore, the committee decided against recommending a tool without sensitivity and specificity data.

Clinical effectiveness of risk tools for reducing VTE

For the review of clinical effectiveness of risk tools, the committee considered all-cause mortality, VTE (symptomatic or asymptomatic), DVT (symptomatic or asymptomatic), PE, fatal PE, major bleeding and quality of life as critical outcomes. The time points for these outcomes were up to 90 days from hospital discharge. The committee considered fatal bleeding, clinically relevant non-major bleeding, heparin-induced thrombocytopenia, hospital length of stay, unplanned readmission and haemorrhagic stroke as important outcomes. The time points for these outcomes were up to 90 days, apart from clinically relevant non-major bleeding up to 45 days from hospital discharge. Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.

Quality of the clinical evidence	**Predictive accuracy of VTE and bleeding risk tools** Fifteen studies were identified looking at risk tools for predicting VTE in surgical or trauma patients. Fourteen papers featured people admitted to hospital (10 for surgery, 3 for trauma and 1 for burn injuries) and one featured people in hospital for day-case surgery. No studies were identified looking at risk tools to predict the risk of major bleeding in surgical or trauma patients. PROBAST was used to assess the risk of bias. All of these studies were at a high or very high risk of bias. Common reasons for this were papers only supplying retrospective validation, papers not reporting a clear definition or method of confirmation for the target condition (VTE, DVT, PE or major bleeding), papers not reporting the time-point for the target condition measurement, or unclear flow and timing between when the risk score was calculated and when the outcome was measured. There were also very low event rates in many of the studies and therefore not a sufficient number of outcome events compared to the number of factors in the risk tool. Many papers also failed to report all the relevant performance measures (sensitivity and specificity). The committee were concerned about the applicability of some risk tools for UK practice due to the setting the tool was originally derived in as well as the location of the validation studies. The committee noted the differences in care settings and medical practices in the US and decided to downgrade any papers from a US setting for indirectness. In particular, the committee highlighted that in the US a much higher proportion of surgical patients are cared for on intensive care wards (ICU), whereas in the UK it is only the very ill (generally those in need of artificial ventilation) who are moved to critical care – so the baseline condition of the two populations would be very different. The committee also considered that the average length of stay in intensive care is around 7 days in the US, compared to a shorter stay of approximately 2–3 days in the UK. **Clinical effectiveness of risk tools for reducing VTE** No randomised controlled trials were identified, therefore observational studies were considered for inclusion in this review. Two observational studies were included in this review (one retrospective cohort study and one before-and-after study). One compared use of the Caprini risk assessment model with no risk assessment tool and one study compared achieving the quality standard of 90% of admissions being assessed with the National VTE Risk Assessment Tool (otherwise known as the Department of Health tool, please see the other considerations section for further detail) with not achieving the quality standard.

	The committee discussed the need for caution when evaluating evidence from quality standard cohort papers and before-and-after studies due to the risk of bias inherent in these designs. The two observational studies provided evidence of very low quality due to risk of bias, primarily based on selection bias and incomplete outcome data. There was imprecision around the effect estimates, and the evidence on the Caprini risk assessment model was also downgraded for indirectness due to the setting being in the US hospital system where practice differs from the UK context.
Trade-off between clinical benefits and harms	Evidence for risk assessment tools came from a very wide range of surgical populations, including abdominal, colorectal, lung, neuro, oesophageal, plastic, and urological surgery; as well as mixed surgical populations, trauma patients and those undergoing day-case surgery (surgical outpatients); all with different associated thrombotic and bleeding risks. The rate of VTE identified in the evidence ranged from 0.33–27.9%. This very large disparity is due to a number of factors including the heterogeneous group of patients and surgery-associated VTE risk; different study designs including RCT, prospective and retrospective cohorts and database/registry studies; and different definitions of the VTE endpoint (asymptomatic or symptomatic). Of the 17 studies reporting on risk tools in surgical and trauma patients only one was undertaken in the UK NHS context. This UK study looked at the National VTE Risk Assessment Tool (hereafter referred to as the National Tool) but was not designed specifically to validate whether this tool can adequately predict risk of VTE or risk of bleeding in the UK surgical population.
	Evidence was identified for a number of VTE risk assessment tools including the Caprini risk assessment model, the American College of Surgeons National Surgical Quality Improvement Programme (ACS NSQIP) Universal Surgical Risk Calculator (not specific to the outcome of VTE) and the Trauma Embolic Scoring System (TESS). No tool was identified to assess the risk of bleeding. The majority of the evidence was found for the Caprini risk assessment model, which is a weighted tool made up of an extensive list of risk factors. Low and very low quality evidence from some highly specific surgical populations (lung cancer, oesophageal cancer, and high-risk abdominal and neurosurgical) suggested that the Caprini risk assessment model reached the committee's thresholds for consideration for both sensitivity and specificity when using cut-offs such as ≥9, ≥10.5 and ≥15. The low and very low evidence from these studies suggested the tools showed moderate discrimination for predicting VTE. Very low quality evidence from the clinical effectiveness review also suggested a reduction in DVT rates when using the Caprini risk assessment model compared to using no formal risk assessment.
	All committee members agreed that risk assessment is a critical part of the pathway for VTE prophylaxis. They also agreed that risk tools are beneficial in this process. Based on the evidence, initial discussions considered whether the Caprini risk assessment model should be recommended over current practice, which is the National Tool. The committee highlighted that there was not thought to be the same issue within the surgical population as that recognised in the medical population (use of the National Tool leading to giving too much prophylaxis). However, they acknowledged that the National Tool has not been validated in any surgical population or in people with trauma. While the evidence suggested the Caprini risk assessment model could be beneficial, the evidence was of low to very low quality and was only validated in highly specific surgical populations and the committee could not be sure that these findings could be generalised to the wider 'mixed' surgical population. There was also concern that the Caprini risk assessment model has almost exclusively been validated only in a US population, and never in the UK population.
	Following decisions on the recommendation for risk assessment in medical patients, the committee discussed whether it was conceptually feasible to recommend different risk assessment tools for the surgical and trauma patients as for the medical patients. They highlighted that the distinction between these two populations is becoming increasingly blurred in the current UK context as surgical

patients will increasingly be older and/or have more medical comorbidities (increasing rates of life-style diseases such as obesity, non-alcoholic fatty liver disease and diabetes). This was also discussed in the context of day-case or outpatient surgery. This covers a mix of minor procedures and as technology improves, and surgeons have access to innovative technologies, surgical time will be reduced and an increasing amount of surgical procedures will become day cases. For this population the VTE and bleeding risk may not necessarily be related to the surgical procedure, but instead be related to the pre-surgical context (for example their medical status).

The committee agreed that it was logical and advisable to have the same risk assessment recommendation for the surgical and trauma population as for the medical population. They also considered that the question of risk assessment tools for the surgical and trauma population was a key priority for future research alongside the research recommendation for risk assessment tools in the medical population. Following stakeholder consultation the committee also decided to acknowledge in the recommendation that the most commonly used VTE risk assessment tool for hospital patients in the NHS is the National Tool (see appendix T).

Trade-off between net clinical effects and costs	One economic study was included. This compared the use of a risk assessment tool based on using ACCP guidelines for surgical patients which were integrated in the hospital electronic system in the form of an e-alert system. The committee discussed the study and noted that, similar to the general medical population in the study, the use of a risk assessment tool for surgical patients was dominant (both more effective and less costly).
	The committee noted that all the risk tools included in the clinical review are generally not associated with any licencing cost although some may require a specific software installation. However, the committee agreed that the evidence for the tools identified was inconclusive and does not support recommending one tool over another. The committee acknowledged that the use of the National Tool for both surgical and trauma patients is currently embedded in NHS practice. However, in contrast to the case in medical patients, the committee did not feel that this tool led to over-prescribing of prophylaxis in the surgical population given the higher baseline risk of VTE compared to general medical patients. The committee also acknowledged that changing from the use of the National Tool to any other tool is likely to have a cost impact to allow the integration of a new tool into practice, which would require robust evidence in terms of clinical and cost effectiveness to support it. The current status of the retrieved evidence did not offer a strong base for recommending any of the identified tools.
	The committee discussed the potential of using the Caprini tool, however there were concerns about the fact that it has not been validated in a UK population and also that it has only been validated in a small number of surgical specialities. After the extensive discussions and voting process outlined in the discussion on risk assessment in medical patients, it was determined that the evidence underpinning the accuracy and effectiveness of all the tools considered for the surgical and trauma populations did not show that one tool is better than the other and a research recommendation was made to allow for future research to address the uncertainty in this area.
Other considerations	The National VTE Prevention Programme was launched in England in 2010 mandating VTE risk assessment in all adult patients admitted to an acute hospital, using a National VTE risk assessment tool.[161] The committee noted that CG92 and the National Tool were published concurrently in 2010, therefore CG92 did not recommend the National Tool by name. However, it was also noted that the recommendation in CG92 and the National Tool is identical.
	The initial goal as part of the Commissioning for Quality Innovation (CQuIN) Framework was to set a 90% target of all patients risk assessed for VTE. This was supported by a financial incentive (CQuIN) payment and within 3 years this goal was increased to 95% which has been exceeded in subsequent years.[161] However the

committee noted that there have been no published studies examining the long-term impact of the National VTE prevention programme, specifically no research has been conducted validating the National Tool's performance at predicting surgical and trauma patients risk of VTE and risk of bleeding. The committee expressed their disappointment in this, especially as this was an area highlighted for further research by the CG92 committee.

The committee made a high-priority research recommendation on risk assessment tools; see appendix R for more details.

The committee discussed giving guidance on the appropriate time to initiate pharmacological prophylaxis following completion of the risk assessment. In particular the committee wanted to highlight that, if using pharmacological prophylaxis, it should be given in a timely manner to ensure that people are not left for too long without it if they happened to be admitted shortly after what is usually a set daily time for doses to be given on a ward. The committee recommend a time point that is in line with current NHS policy on time to consultant review of acute inpatients. This standard states that all emergency admissions must be seen and have a thorough clinical assessment by a suitable consultant as soon as possible, but at the latest within 14 hours from the time of admission to hospital.[134] The committee agreed that recommending a similar timeframe within which pharmacological prophylaxis should be given (if indicated by risk assessment) makes logical clinical sense and will ensure clinical care is not delayed.

6 Reassessment of VTE and bleeding risk

6.1 Introduction

After admission or a procedure at hospital a person's medical condition will usually change. As a consequence of this change their risk of VTE and bleeding may also change. The last version of the guideline (CG92)[124] recommended patients were reassessed every 24 hours. This update reviewed the evidence for the effectiveness of reassessment of VTE and bleeding risk to establish if this time point was appropriate for some or all patients.

6.2 Reassessment of risk for hospital admissions

6.2.1 Review question: How effective is reassessment of people who are admitted to hospital?

For full details see review protocol in appendix C.

Table 54: PICO characteristics of review question

Population	Adults (aged 16 or over) admitted to hospital who have been reassessed
Intervention(s)	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)
Comparison(s)	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) • 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)

6.2.2 Clinical evidence

No relevant clinical studies comparing derived and validated risk tool with no risk tool for risk reassessment were identified in people who are admitted to hospital. See the study selection flow chart in appendix E and excluded studies list in appendix N.

6.2.3 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

6.2.4 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

No relevant economic evaluations were identified.

6.3 Reassessment of risk for day procedures

6.3.1 Review question: How effective is reassessment of people who are having day procedures at hospital?

For full details see review protocol in appendix C.

Table 55: PICO characteristics of review question

Population	Adults (aged 16 or over) people who are having day procedures at hospital
Intervention(s)	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)
Comparison(s)	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) • 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)

6.3.2 Clinical evidence

No relevant clinical studies comparing derived and validated risk tool with no risk tool for risk reassessment were identified in people who are having day procedures at hospital. See the study selection flow chart in appendix E and excluded studies list in appendix N.

6.3.3 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

6.3.4 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

No relevant economic evaluations were identified.

6.4 Recommendations and link to evidence

Recommendations	1.1.8 Reassess all medical, surgical and trauma patients for risk of VTE and bleeding at the point of consultant review or if their clinical condition changes. [2018]
Research recommendation	None
Relative values of different outcomes	The committee considered 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), and quality of life (validated scores) (duration of study) as critical outcomes. 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), unplanned readmission (duration of study) and haemorrhagic stroke (duration of study) were considered important outcomes. Please see section 4.4.3 in the methods chapter for further detail explaining prioritisation of the critical outcomes.
Quality of the clinical evidence	No clinical evidence was identified.
Trade-off between clinical benefits and harms	The committee acknowledged the importance of re-assessing VTE and bleeding risk to guide prophylaxis provision or stopping decisions, which in turn would optimise their use. No evidence was found for the effectiveness of any VTE risk tool specifically for reassessment, and the committee did not consider that there was enough evidence

	for the accuracy or clinical effectiveness of any particular VTE or bleeding risk assessment tool from the reviews covering initial risk assessment to make a specific recommendation. Therefore the committee made a consensus recommendation that the VTE and bleeding risk for people admitted to hospital and those having day procedures should be reassessed at the point of senior review or if their clinical condition changes. The committee considered that undertaking the reassessment at the point of senior review or more frequently if there is a change in clinical condition would allow tailoring the need and the frequency of re-assessment to the individual clinical condition and optimise outcomes. The committee acknowledged that individuals undergoing day procedures attend the hospital for a short period of time and in the majority of cases are ambulant. Hence, reassessment would only be required if their clinical condition is likely to change.
Trade-off between net clinical effects and costs	No relevant economic studies were identified. The committee noted that the only resource that would be required for re-assessment is staff time; which would be minimal (approximately 10 minutes of a junior doctor's time). The committee also noted that current practice is for re-assessment to be undertaken within 24 hours, which requires staff time, without evidence of cost-effectiveness. Hence the committee considered that it is not possible to mandate 24 hours as the time of review. Reassessment at the time of senior review was considered to be the most convenient and least resource intensive option as the reassessment would be done as part of a scheduled review.
Other considerations	None.

7 Risk assessment for pregnant women and women up to 6 weeks post-pregnancy

7.1 Introduction

Pregnancy and the postpartum period are risk factors for VTE. This review aims to assess the risk of VTE and major bleeding in pregnant women, and women who have given birth in the previous 6 weeks, who are admitted to hospital and midwife units for reasons related to their pregnancy, and/or for treatment for other conditions un-related to pregnancy. To do this the review examines i) the predictive accuracy of risk tools, ii) the clinical and cost effectiveness of risk tools and iii) the effectiveness of reassessment.

7.2 Prognostic review question: What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE or 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?

For full details see review protocols in appendix C.

Table 56: PICO characteristics of prognostic review question

Question	What is the accuracy of individual risk assessment or predication tools in predicting the likelihood of VTE or 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?
Population	Pregnant women who are admitted to hospital and midwife units including up to 6 weeks after giving birth.
Risk tool	Derived and (externally or temporally) 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) OR • Major bleeding (up to 90 days)
Outcomes (in terms of predictive test accuracy, calibration)	Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values) • 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

7.2.1 Clinical evidence

Only one study relating to the use of risk tools for pregnant women was included in the review. This study assessed the accuracy of a risk prediction model in predicting the likelihood of VTE in postpartum women. [183] This study is summarised in Table 57.

Table 57: Summary of studies included in the review

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Accuracy of risk tools for VTE					
Sultan 2016 [183]	Risk prediction model (development and validation) for VTE in postpartum women.	n=498918 women with 662387 births. Pregnancies in women with no history of VTE resulting in a live birth or stillbirth between 1 July 2005 and 31 December 2011. Mean (SD) age: 30 (5) years Gender: all women Sweden	VTE (within six weeks after birth): a diagnosis of venous thromboembolism was considered valid if it 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. C-statistic Sensitivity and specificity at thresholds derived by using existing UK and Swedish guidelines as reference standard with those taking pharmacological thromboprophylaxis as prevalence data. Sensitivity and specificity based on arbitrary risk thresholds.	n=521 (0.00078%)	Retrospective cohort (registry data)
Accuracy of risk tools for major bleeding					
No studies included					
Clinical and cost-effectiveness of risk assessment					
No studies included					
Clinical and cost-effectiveness of risk re-assessment					
No studies included					

7.2.2 Discrimination

7.2.2.1 VTE in postpartum women

Table 58: **Clinical evidence profile: risk tools for predicting VTE in postpartum women**

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Risk prediction model	1	662387	Very serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Top 1% risk score (threshold 41.2) 9.0 (6.7-11.8)	Top 1% risk score (threshold 41.2) 99.0 (98.9-99)	0.73 (0.71-0.75)	LOW
							Top 5% risk score (threshold 19.7) 26.7 (22.9-30.7)	Top 5% risk score (threshold 19.7) 95.0 (95.0-95.1)		
							6% cut-off [b] 30.3 (26.4-34.5)	6% cut-off [b] 93.8 (93.7-93.9)		
							Top 10% risk score (threshold 14.0) 35.5 (31.4-40.0)	Top 10% risk score (threshold 14.0) 90.0 (90.0-90.1)		
							Top 20% risk score (threshold 9.8) 53.4 (50.0-57.7)	Top 20% risk score (threshold 9.8) 80.0 (79.9-80.1)		

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (%)	Specificity (%)	C-statistic	Quality
							Top 25% risk score (threshold 8.7) 59.5 (55.1-63.7)	Top 25% risk score (threshold 8.7) 75 (74.9-75.2)		
							35% cut-off [c] 68.1 (63.9-72.1)	35% cut-off [c] 65.1 (64.9-65.2)		

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision making. The committee set the following thresholds as an acceptable level to recommend a test: sensitivity 80% and specificity 60%.
(c)   Risk of bias was assessed using the PROBAST checklist items relating to risk of bias
(d)   Threshold based on number of pregnant women warranting thromboprophylaxis according to 2011 Swedish Association of Obstetricians and Gynaecologists (SFOG) guidelines.
(e)   Threshold based on number of pregnant women warranting thromboprophylaxis according to 2015 UK Royal College of Obstetricians and Gynaecologists (RCOG) guideline[168]

7.2.3 Calibration

No calibration evidence identified.

7.2.4   Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

7.3 Intervention 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?

For full details see review protocols in appendix C.

Table 59: PICO characteristics of risk tools as an intervention review question

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?
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 of pregnancy) Target condition: VTE/DVT/PE/major bleeding
Risk tool	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 types	Systematic reviews of RCTs or RCTs. If no RCTs then observational cohort data.

7.3.1 Clinical evidence

No studies were included that compared risk assessment with no risk assessment. See the study selection flow chart in appendix E, study evidence tables in appendix H, and excluded studies list in appendix N.

7.3.2 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

7.4 Reassessment 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?

For full details see review protocols in appendix C.

Table 60: PICO characteristics of reassessment of risk in pregnant women

Question	How effective is reassessment of the risk of VTE and/or bleeding of pregnant women who are admitted to hospital or midwife units?
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 of pregnancy) Target condition: VTE/DVT/PE/major bleeding
Risk tool	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 (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 types	Systematic reviews of RCTs or RCTs. If no RCTs then observational cohort data.

7.4.1 Clinical evidence

No studies were included for risk reassessment. See the study selection flow chart in appendix E, study evidence tables in appendix H, and excluded studies list in appendix N.

7.5   Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

7.6   Evidence statements

Clinical

Low quality evidence from one study (n=498,918 women with 662,387 births) suggested that the risk prediction model had a moderate ability to distinguish between those postpartum women who are at risk or not at risk of experiencing a VTE within six weeks after giving birth, based on the c-statistic. However, the tool showed poor sensitivity at predicting those at risk of having the event with none of the sensitivities reported reaching the committees pre-specified threshold (primary measure for decision-making: sensitivity 80%). Sensitivities ranged from 9% for predicting the top 1% at risk to 68.1% for predicting the top 35% at risk. The tool showed specificities for predicting those not at risk for VTE ranging from 99% for the top 1% and 65.1% for the top 35%. Specificities at all cut-offs (including variance) were above the committee's pre-specified threshold of 60%.

Economic

No relevant economic evaluations were identified.

7.7   Recommendations and link to evidence

Recommendations	**1.1.9 Assess all women on admission to hospital or a midwife-led unit if they are pregnant or gave birth, had a miscarriage or had a termination of pregnancy in the past 6 weeks, to identify their risk of VTE and bleeding. Use a tool published by a national UK body, professional network or peer-reviewed journal. The most commonly used risk assessment tool was developed by the Royal College of Obstetricians and Gynaecologistsᵒᵒᵒ (See Appendix U) [2018]**
	
	1.1.10 Reassess risk of VTE and bleeding, and assess the need for thromboprophylaxis for all women:
	• **within 6 hours of giving birth, having a miscarriage or having a termination of pregnancy or**
	• **if their clinical condition changes and they:**
	   - are pregnant or
	   - gave birth, had a miscarriage or had a termination of pregnancy within the past 6 weeks. [2018]

Research	**1. What is the accuracy of individual risk assessment tools in predicting the**

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ooo   Reproduced from: Royal College of Obstetricians and Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG, 2015, with the permission of the Royal College of Obstetricans and Gynaecologists.

recommendation	risk of VTE and risk of bleeding in pregnant women and women up to 6 weeks post-pregnancy admitted to hospital?
Relative values of different outcomes	The committee was interested in the prognostic accuracy of tools to predict risk of VTE in pregnant and postpartum women, including termination of pregnancy within the past 6 weeks. The committee intended to use the tool to identify people who are at higher risk of VTE when admitted to hospital (at any stage of pregnancy) who would benefit from prophylaxis.
	The committee agreed that the priority of such a tool would be a high sensitivity to avoid missing those at high risk of VTE and consequently failing to offer them prophylaxis (reduce false negatives) alongside consideration of a reasonably acceptable corresponding specificity. The committee set minimum thresholds for the acceptability of a risk prediction tool in this population as sensitivity and specificity values above 90% and 60% respectively.
Quality of the clinical evidence	The evidence is sourced from a single retrospective study judged to be at very serious risk of bias for the predictive accuracy outcome. This is due to flow and timing issues between the assessment of risk factors and the measurement of VTE outcome. There was no further down-grading for inconsistency or indirectness. As sensitivity was the primary measure for decision-making, imprecision was judged on the confidence interval around the sensitivity estimates. The confidence intervals were tight across all sensitivity thresholds reported, so therefore no serious imprecision was identified.
Trade-off between clinical benefits and harms	Pregnancy is a highly prothrombotic state and temporary illness and/or immobilisation will lead to a further increased risk of VTE. All committee members agreed that risk assessment is a critical part of the pathway for VTE prophylaxis. They also agreed that risk tools are beneficial in this process.
	In discussion with the obstetric subgroup, the committee considered that basing assessment of risk on the current (2015) RCOG guidelines[168] may result in offering an unnecessarily large proportion of pregnant and postpartum women VTE prophylaxis (35% according to the included study[183]). The committee noted this concern and appreciated that a reduction in the number of women unnecessarily having thromboprophylaxis is important but needs to be balanced against the risk of getting VTE. The subgroup discussed the trend in some sectors to over-medicalise pregnant and postpartum women. However, evidence was identified for only one risk model and this was specifically for postpartum women within 6 weeks of giving birth. This evidence was of low quality showing only moderate discrimination and poor sensitivity at predicting those at risk of experiencing VTE.
	The subgroup and committee discussed the CG92 recommendation where separate VTE risk factors were noted for pregnant women as a subgroup of the population covered by the National VTE Risk Assessment Tool. However, they acknowledged that the risk assessment recommended in CG92 has not been validated in a UK population of pregnant and post-pregnancy women. When considering the risk factors previously listed the committee paid particular attention to the age and obesity risk factors that were within the list set out in CG92. They considered that these were two factors that have significantly changed in the current population compared to that in 2009. The group considered it may be unnecessary to recommend VTE prophylaxis if the woman's only risk factor was age > 35 years. However the group acknowledged evidence that pregnant women admitted to hospital aged ≥35 years were at increased risk of VTE[2]. The subgroup acknowledged that the average BMI has increased since the 2009 recommendation was made. Over a third of pregnancies are >30 kg/m^2 and this is rising which reflects rising BMI in the general population[44]. The committee highlighted these two risk factors in particular as an example of The National Tool being interpreted as a 'tick-box exercise', where clinicians view it as a unweighted checklist of risk factors; if you tick one box (a single risk factor) that equates to a high VTE risk and this automatically results in prophylaxis being offered. Most importantly this fails to highlight the clinical

	judgement that must come into play in order to consider whether individual risk factors lead to an overall increased risk, and the balance of this with any bleeding risk factors or other contraindications
	The committee appreciated that some risk factors for VTE are important in this population (including age and BMI) and noted that they should be considered when pregnant women are risk assessed. The committee determined that in the absence of evidence it was logical and advisable to be consistent with the approach used for the medical, and surgical and trauma recommendations and have a similar risk assessment recommendation for the population of pregnant and post-pregnancy women. They also agreed that the question of risk assessment tools for pregnancy and post-pregnancy women was a key priority for future research alongside the research recommendation for risk assessment tools in the medical, surgical and trauma population. Following stakeholder consultation the committee also decided to acknowledge in the recommendation that the most commonly used VTE risk assessment tool for obstetrics in the NHS is the tool recommended in the Royal College of Obstetricians and Gynaecologists (Thrombosis and Embolism during Pregnancy and the Puerperium, Reducing the Risk (Green-top Guideline No. 37a), published in 2015) and have reproduced this in appendix U .
	There are multiple time-points at which risk would have to be assessed and reassessed as the risk profile of the woman changes. It is particularly important to re-assess risk within the 6-hour window postpartum as the bleeding risk would have changed from pre-labour state, and to allow time to check post-delivery outcome.
Trade-off between net clinical effects and costs	No economic evidence was identified. Relevant unit costs of subsequent prophylaxis were provided to aid the committee's discussions (see appendix Q). The committee considered risk assessment of pregnant and postpartum women admitted to hospitals and midwife-led units as an important screening step to identify women for whom offering thromboprophylaxis would be cost-effective. It was acknowledged that current levels of prophylaxis provision and the recommendations of the RCOG Green Top guideline represent a high cost to the NHS with limited evidence of benefit. Hence, the committee considered that risk assessment would allow the identification of those women at high risk of hospital-acquired VTE for whom the provision of thromboprophylaxis would represent value for money.
	The committee acknowledged that this initial screening would need to reliably identify those women who may go on to develop costly VTE events if not given prophylaxis, hence; high sensitivity was seen as the more important criterion. This would ensure that the number of false negatives is minimised. Reasonable levels of specificity were also considered to be important to minimise false positives who will go on to receive prophylaxis unnecessarily and may develop side effects such as major bleeding with its associated high cost and loss in quality of life. However, no such tool could be identified. In absence of any validated risk assessment tool, relying on identifying individual risk factors might be justified. However, some risk factors were considered to be highly prevalent, resulting in provision of costly prophylaxis to an unnecessarily large number of women.
	The committee agreed that standardising practice with that in medical and surgical admissions would be important; hence, a similar recommendation to those populations was adopted. An overarching research recommendation was also agreed as it was considered that the value of obtaining further information on the choice of a risk tool would outweigh the benefits of implementing an approach whose effectiveness and cost effectiveness are highly uncertain.
Other considerations	The committee and obstetric subgroup agreed that even though a specific risk assessment tool was not recommended there are particular risk factors that are important for this population that will likely feature in published VTE risk assessment tools for pregnant women. These factors could include: expected to have significantly reduced mobility, dehydration, major thrombophilias including antiphospholipid antibodies, antithrombin deficiency, or compound heterozygous or

homozygous for any other thrombophilia (but not heterozygous factor V Leiden or prothrombin 20210), and pregnancy-related risk factors such as assisted reproduction techniques [ART], ovarian hyperstimulation, hyperemesis gravidarum, multiple pregnancy or pre-eclampsia).

The committee are aware that the RCOG risk tool is commonly used in practice, if clinicians have any concerns around risk factors (such as those listed above), reference can be made to the RCOG risk tool. The RCOG tool as outlined in appendix U.

The committee made a high-priority research recommendation on risk assessment tools; see appendix R for more details.

8 Giving information and planning for discharge

8.1 Introduction

Medical professionals have a responsibility to inform patients under their care about proposed interventions. In this context it means providing information on venous thromboembolism (VTE) risk, the optimal methods to prevent this, including verbal and written information, the consequences of not receiving prophylaxis, and possible side effects of the prophylactic intervention. This opportunity for discussion should be made available before provision of prophylaxis, unless this is not clinically possible (for example unconsciousness) or when any delays could be seriously detrimental.

Good communication between the healthcare professionals and the patient is essential. In the context of this guideline, patients may be newly admitted to the hospital and often find the situation overwhelming. This is not the best time to assimilate complex information and make decisions, and healthcare professionals should take this into account when communicating with patients. Patients should be encouraged to ask questions at any point during their stay and healthcare professionals may have to check that they understand the information from time to time. For elective patients information can also be given in advance.

One of the main classes of drugs used for thromboprophylaxis is heparin; either low molecular weight heparins (LMWH) or unfractionated heparin (UFH). Heparin is a sulphated glycosaminoglycan derived from animal tissues, and those marketed in the UK are principally of porcine origin. Using animal derived products may be of concern to patients of certain religious or personal beliefs. Therefore, healthcare professionals should be prepared to discuss these concerns with the patients (or their caregivers) and provide them with information to help them to address any ethical or religious concerns. Depending on the individual clinical condition of the patient, the synthetic alternatives to heparin may be less suitable or have disadvantages. Clinicians should ensure that patients are aware of these issues.

8.2 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?

For full details see review protocol in appendix C.

Table 61:   Characteristics of review question

Objective	To identify the barriers and facilitators to the provision of information about VTE and VTE prophylaxis to giving people who are admitted to hospital, having day procedures or outpatients post-discharge, and their family or carers
Population and setting	Adults and young people (16 years and older) who are: • Admitted to hospital • 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
Review strategy	Synthesis of qualitative research. Results presented in narrative and table format. Quality of the evidence will be assessed by a GRADE CerQual approach for each review finding.

8.3 Qualitative evidence

8.3.1 Methods

We searched for qualitative studies exploring 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.

Four qualitative studies were included in the review;[8, 111, 123, 138] these are summarised in Table 62 below. The aim of all the studies was to explore patients' experiences, perceptions and understanding of VTE prophylaxis. All studies used either face-to-face or telephone semi-structured interviews as the data collection method. Key findings from these studies are summarised in Section 8.3.2 below. See also the study selection flow chart in appendix E, study evidence tables in appendix H, and excluded studies lists in appendix N.

8.3.2 Summary of included studies

Table 62: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Apenteng 2016[8]	Face-to-face semi-structured interviews using framework analysis	n=31 People classed by hospital staff as being a high risk of developing VTE during a recent hospital admission (orthopaedic surgery 58.1%, gastrointestinal surgery 22.6%, other surgery 19.3%) Males and females: 17:14 UK	To explore patients' awareness of VTE and their experience with VTE prophylaxis	
May 2006[111]	Semi-structured interviews which were then analysed for emergent themes individually and then	n=12 People who had elective surgery (33%) or were emergency admissions to	To explore patients' experiences of AES (anti-embolism stockings), to ascertain their perceptions about	

Study	Design	Population	Research aim	Comments
	as a group	gynaecology, obstetrics, general surgery, orthopaedics and stroke medicine (66%) Gender not reported UK	use and care, and identify any limitations in the information currently provided	
Najafzadeh 2015[123]	In person or telephone phone semi-structured interviews using the constant comparative method of analysis	n=12 People who had undergone hip (75%) or knee (25%) replacement surgery Males and females: 3:9 United States	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	
Noble 2006[138]	Semi-structured interviews using a thematic analysis	n=28 People with metastatic cancer or primary brain tumour, who had received LMWH thromboprophylaxis for at least 5 consecutive days UK	To find out what in patients with advanced cancer who are receiving palliative care think about the effect of thromboprophylaxis and whether heparin is an acceptable intervention	

8.3.3 Qualitative evidence synthesis

Table 63: Review findings

Main findings	Statement of finding
Understanding of VTE and VTE prophylaxis	Participants reported a mixed understanding of VTE and of VTE prophylaxis
Information and information needs	Participants reported receiving and retaining limited information from few sources, and discussed the desire for more information
Beliefs about benefits of thromboprophylaxis	Although most participants were aware of the benefits of antithrombotic therapy, some also had false beliefs about benefits
Beliefs about the risks of thromboprophylaxis	Only half of participants considered serious bleeding as a possible side effect of antithrombotic therapy
Factors influencing patients' decision to use antithrombotic medications	A combination of implicit trust, balance of benefits against risks, and the acceptability of prophylaxis led to the decision for patients to use VTE prophylaxis

8.3.3.1   Narrative summary of review findings

Review finding 1: Patients' understanding of VTE and VTE prophylaxis

Participants reported a mixed understanding of VTE, with only some demonstrating a clear understanding of DVT and PE. Although most participants were aware that VTE was undesirable and could have serious consequences, many participants were not aware of the symptoms of DVT or PE, such as painful swollen legs, or could only describe symptoms vaguely. Some participants were aware of the risk of blood clots following surgery, but did not refer specifically to the terms DVT or PE. Conversely, many participants were able to demonstrate a basic understanding of myocardial infarction and stroke.

Participants similarly demonstrated a mixed understanding of VTE thromboprophylaxis. Whilst most understood the purpose of treatment with LMWH and AES (anti-embolism stockings), and were aware of why they might be at risk of VTE, some participants did not fully understand the purpose or could not relate it to their circumstances. For instance some participants did not understand AES as a prophylactic measure rather than treatment, and others demonstrated incorrect beliefs about how to use and wear AES.

This may be partially explained by the fact that one third of participants were not informed about the potential complications of prophylactic treatment prior to surgery. This demonstrates the potential need for the provision of more patient information, however it is worth noting that all participants were operated on by one of two surgeons, and therefore this finding may be biased and not reflective of other practices and settings.

Explanation of quality assessment: moderate methodological limitations; minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to the majority of evidence coming from a population of patients who have had a hip or knee replacement surgery or incurable cancer, and therefore representing a small sub-set of the population of interest for the review question. All evidence is based on patients and there is no evidence from family, carers, or health care professionals; serious concerns about adequacy, due to the fact that all evidence is from a small number of studies.

Review finding 2: Information and information needs

For some participants, knowledge of VTE appeared to be based the work up they received during their hospital admission, however for many it was based on media coverage, long haul flight health information and, for some, previous personal or limited secondary experiences. Many participants reported that they were not informed about the potential complications of prophylactic treatment prior to surgery. Many also reported that they did not receive information about how to use AES, everyday care of AES such as how to wash them and when to take them off, and some also reported receiving limited information regarding exercise and physiotherapy. Of those who were provided information, many reported that either they received information that was conflicting and inconsistent, or that they could not remember what was given either verbally or in writing. Similarly, those that reported having been given a leaflet could remember very little of what it said.

Whilst some participants reported that more information would be of value, others thought that there was no need for additional information as they perceived it as common sense. Some participants also expressed the belief that any necessary information would have been supplied by nurses. Those that did express a desire for more information identified several areas for education, including how VTE prophylaxis works, clarity on AES use, information on symptoms of blood clots, and information about the side effects of prophylaxis.

Explanation of quality assessment: moderate methodological limitations; minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due

to the majority of evidence coming from a population of patients who have had a hip or knee replacement surgery or incurable cancer, and therefore representing a small sub-set of the population of interest for the review question. All evidence is based on patients and there is no evidence from family, carers, or health care professionals; serious concerns about adequacy, due to the fact that all evidence is from a small number of studies.

Review finding 3: Beliefs about benefits of thromboprophylaxis

Participants were aware of the benefits of antithrombotic therapy and described these in terms of reducing the risk of blood clots and thinning the blood to help blood flow. However, many participants had a limited understanding of the rationale of this, and some also had false beliefs that antithrombotic therapy could also reduce the risk of a stroke or myocardial infarction. This indicates that participants may not have understood information provided to them about benefits of antithrombotic treatment, or may be making assumptions based on a lack of information.

Explanation of quality assessment: moderate methodological limitations; minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to the majority of evidence coming from a population of patients who have had a hip or knee replacement surgery or incurable cancer, and therefore representing a small sub-set of the population of interest for the review question, further all evidence is based on patients and there is no evidence from family, carers, or health care professionals; serious concerns about adequacy, due to the fact that all evidence is from a small number of studies, and also because there was very limited elaboration of the theme.

Review finding 4: Beliefs about the risks of thromboprophylaxis

Participants were aware of the risk of excess bleeding and bruising as a result of an injury such as a cut, and described this as a consequence of antithrombotic therapies thinning the blood. However, only some participants discussed serious bleeding, such as internal bleeding and haemorrhage, as a possible side effect of antithrombotic therapy.

Explanation of quality assessment: moderate methodological limitations; minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to the included study only representing patients who have had a hip or knee replacement surgery, and therefore a small sub-set of the population of interest for the review question, further all evidence is based on patients and there is no evidence from family, carers, or health care professionals; serious concerns about adequacy as all evidence for the finding is from a single study, and also because there was very limited elaboration of the theme, despite the large number of examples and extracts from the transcripts.

Review finding 5: Factors influencing patients' decision to use thromboprophylaxis

Participants reported trusting their physician's expertise as the primary reason for their decision to use antithrombotic medication as prescribed. Participants described having confidence in their doctors when being prescribed medication and as a result of experiencing their surgical skills. Many participants also discussed balancing the benefits against the risks when considering thromboprophylaxis. For instance, some participants demonstrated the perception that the risk of bleeding was not substantially high as therapy was short term, and because bleeding was perceived as an event that could be monitored, controlled and reversed by stopping or modifying medication. This led to the belief that bleeding events were less serious and consequential compared to blood clots. Conversely, participants believed that the risk of blood clots and their consequences were more significant, and many participants were willing to trade off an increased risk of bleeding for a reduced VTE risk. Those that did have serious concerns about bleeding due to factors such as family bleeding history or bleeding disorder reported that this concern was not discussed with their doctors

as they believed that there was no other option, and that their physician had carefully considered their individual profile to assure benefits outweighed risks, again highlighting the role of trust in physicians. A third factor identified by participants was the acceptability of thromboprophylaxis and LWMH in particular. Many felt that LMWH prophylaxis was neither pleasant nor unpleasant, and acknowledged that it was part of usual practice, and therefore found it acceptable.

Explanation of quality assessment: moderate methodological limitations; minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to the majority of evidence coming from a population of patients who have had a hip or knee replacement surgery or incurable cancer, and therefore representing a small sub-set of the population of interest for the review question. Further, all evidence is based on patients and there is no evidence from family, carers, or health care professionals; moderate concerns about adequacy, due to the fact that all evidence is from a small number of studies, , however the data for this finding was much more rich.

8.3.4 Qualitative evidence summary

Table 64: Summary of evidence

Study design and sample size			Quality assessment		
No of studies contributing to the finding	Design	Finding	Criteria	Rating	Overall assessment of confidence
Patients' understanding of VTE and VTE prophylaxis					
4	Semi-structured interview	Participants reported a mixed understanding of VTE and of VTE prophylaxis	Limitations	Moderate limitations	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance	
			Adequacy	Serious concerns about adequacy	
Information and information needs					
4	Semi-structured interview	Participants reported receiving and retaining limited information from few sources, and discussed the desire for more information	Limitations	Moderate limitations	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance	
			Adequacy	Serious concerns about adequacy	
Beliefs about benefits of thromboprophylaxis					
3	Semi-structured interview	Although most participants were aware of the benefits of antithrombotic therapy, some also had false beliefs about benefits	Limitations	Moderate limitations	VERY LOW
			Coherence	No or very minor concerns about	

No of studies contributing to the finding	Design	Finding	Criteria	Rating	Overall assessment of confidence
Study design and sample size			**Quality assessment**		
				coherence	
			Relevance	Minor concerns about relevance	
			Adequacy	Serious concerns about adequacy	
Beliefs about the risks of thromboprophylaxis					
1	Semi-structured interview	Only half of participants considered serious bleeding as a possible side effect of antithrombotic therapy	Limitations	Moderate limitations	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Serious concerns about adequacy	
Factors influencing patients' decision to use thromboprophylaxis					
2	Semi-structured interview	A combination of implicit trust, balance of benefits against risks, and the acceptability of prophylaxis led to the decision for patients to use VTE prophylaxis	Limitations	Moderate limitations	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy	

8.4 Economic evidence

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

8.5 Evidence statements

Clinical

Please refer to section 8.3.3.1 for the narrative summary of review findings.

Economic

No relevant economic evaluations were identified.

8.6 Recommendations and link to evidence

Recommendations	1.2.1 On admission ensure that people understand the reason for having a risk assessment for VTE and bleeding. [2018]
	1.2.2 For people admitted to hospital who are at increased risk of VTE, give them and their family members or carers (as appropriate) verbal and written information on the following before offering VTE prophylaxis:
	• the person's risks and possible consequences of VTE
	• the importance of VTE prophylaxis and its possible side effects – for example, pharmacological prophylaxis can increase bleeding risk
	• the correct use of VTE prophylaxis – for example, anti-embolism stockings, intermittent pneumatic compression
	• how people can reduce their risk of VTE (such as keeping well hydrated and, if possible, exercising and becoming more mobile). [2018]
	1.2.3 Be aware that heparins are of animal origin and this may be of concern to some people[ppp]. Discuss the alternatives with people who have concerns about using animal products, after discussing their suitability, advantages and disadvantages with the person. [2018]
	1.2.4 As part of the discharge plan, give patients and their family members or carers (as appropriate) verbal and written information on:
	• the signs and symptoms of deep vein thrombosis (DVT) and pulmonary embolism (PE)
	• how people can reduce their risk of VTE (such as keeping well hydrated and, if possible, exercising and becoming more mobile)
	• the importance of seeking help if DVT, PE or other adverse events are

[ppp] See Religion or belief: a practical guide for the NHS.

suspected. [2018]

1.2.5 Give people discharged with VTE prophylaxis and their family members or carers (as appropriate) verbal and written information on:

- **the importance of using VTE prophylaxis correctly (including the correct administration and disposal of pharmacological prophylaxis)**
- **the importance of continuing treatment for the recommended duration**
- **the signs and symptoms of adverse events related to VTE prophylaxis**
- **the importance of seeking help and who to contact if people have problems using VTE prophylaxis. [2018]**

1.2.6 Ensure that people who are discharged with anti-embolism stockings:

- **understand the benefits of wearing them**
- **understand the importance of wearing them correctly**
- **understand the need to remove them daily for hygiene purposes**
- **are able to remove and replace them, or have someone available who will be able to do this for them**
- **know what to look for if there is a problem – for example, skin marking, blistering or discolouration, particularly over the heels and bony prominences**
- **know who to contact if there is a problem**
- **know when to stop wearing them. [2018]**

1.2.7 Ensure that people who are discharged with pharmacological and/or mechanical VTE prophylaxis are able to use it correctly, or have arrangements made for someone to be available who will be able to help them. [2018]

1.2.8 Notify the person's GP if the person has been discharged with pharmacological and/or mechanical VTE prophylaxis to be used at home. [2018]

Research recommendation	**None**
Findings identified in the evidence synthesis	Five themes were identified in this review. All of these themes related to the understanding of VTE and VTE prophylaxis, the provision of information and how patients understand and make decisions based on that information. The findings indicate that patients may not always receive sufficient information, or understand and retain the information they are given at the time (they may be anxious due to the planned treatment, for example operation, or under stress during or after discharge). The findings also highlight the high level of implicit trust that patients may put in healthcare professionals, and the need to actively involve and encourage patients to participate in discussions about their care and medication.
Quality of the evidence	The committee noted that there is far less evidence discussing patient preference for information with respect to VTE prophylaxis than that of patient information about VTE treatment, or post-VTE patient experience. It was noted that there is a greater

awareness about thrombosis, DVT and PE in the UK than in other countries in the world.[197]

Four studies were included in this review, from which five findings were identified. All findings were judged to be very low in terms of the overall assessment of confidence. For all findings, there was judged to be moderate concerns regarding methodological limitations, due to a lack of reflection on the role of the researcher, and limited details reported about the context of the research and analysis method. The findings were also downgraded due to concerns about relevance, as for some findings the evidence came from a population of people undergoing hip or knee replacement only or a population of palliative care cancer patients, both of which constitute a very small proportion of the population of interest. Findings were also only from patients, and no data were identified from family, carers or healthcare professionals. For four of the five findings, there were serious concerns about adequacy, and for one finding there were moderate concerns about adequacy. This was due to the fact that all evidence was from only three studies. Furthermore, for three of the findings it was judged that there was insufficient exploration and elaboration of the themes, resulting in sparse data.

Trade-off between benefits and harms	The committee noted that these findings came from four studies of a total of 83 participants, in addition the committee also referred to their clinical experience and expertise when discussing recommendations.
	The committee noted that the new evidence identified since CG92 suggests a need for more patient information, however there was very little evidence that detailed what specific patient information needs to be provided, or how to impart this information. The committee were also aware that the studies conducted in 2006 may not reflect patients' experiences now due to the increased use of social media as a platform for sourcing and distributing information and support. The committee noted the difference between VTE prophylaxis and VTE treatment in terms of the patient experience and what may be important to patients in terms of the information provided.
	Based on clinical experience, the committee emphasised the importance of patient involvement and inclusion in decision making as soon as possible, and of providing patients with the means to be actively involved in their treatment, such as providing patients with information about what they can do to reduce their risk. The committee discussed the need to give clear and unambiguous information in both verbal and written form and the importance of sign-posting someone for them to contact at a later date if needed. The committee recognised that certain age groups may tend to prefer information in particular formats, and the clinicians need to be sensitive to literacy levels and translation requirements. Not all hospitals have a specific discharge team in place to deliver information on discharge.
	The level of detail provided will depend on individual patient preferences. The committee determined that all patients needed the basic information about how to spot the signs and symptoms of VTE and who to contact if they noticed these symptoms. This was considered to be the most important information people can receive: What can I do? What might happen? And what can I do if that happens?
	Healthcare professionals should be sensitive to the level of information that the patient wants to receive. It may be a balancing act as clinicians are responsible for giving all patients information about how to reduce their VTE risk; however it was raised that some patients may be unduly worried by receiving information about risk of VTE and risk of bleeding.
Trade-off between net effects and costs	No relevant economic studies were included, as this is a qualitative review focused on the content of the information provided to patients. The committee considered that providing adequate information and support, or communicating with patients in an appropriate manner is likely to require low cost interventions and provide benefit

	to patients, so is usually cost-effective.
Other considerations	With respect to providing information to patients to allow them to feel empowered the committee discussed that in specific populations, such as those with cancer-associated thrombosis, there is evidence that when given adequate information about recognising the signs and symptoms of thrombosis, patients will access help in a timely manner which reduced mortality.[137] The committee agreed that this would be just as relevant to other patient populations, such as post-surgical populations where the symptoms of thrombosis may be attributed to the illness/surgery and therefore the patient may delay accessing VTE advice.
	The committee pointed out the importance of using plain English when giving patients information about VTE, particularly with respect to the word prophylaxis and possible alternatives (for example treatment given to prevent a blood clot).
	While it is important to offer patients alternatives if there are concerns about using animal based products, it is also important that patients are aware of the clinical benefits or disadvantages (if any) of using these alternative products. If religious beliefs are a source of concern, the patient should be aware of the official stand of religious bodies about the product. Patients will only be able to make a good decision if they have a complete picture of the pros and cons of using these products. Where information is available, it will be useful to direct the patient to these information sources. There is information for patients with specific concerns, for example: "Porcine Derived Products" booklet which is referred to in the Department of Health document titled "Religion or belief: a practical guide for the NHS" (available from http://webarchive.nationalarchives.gov.uk/20130123195548/http://www.dh.gov.uk /en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_0931 33) .

9 General VTE prevention for everyone in hospital

9.1 Summary of the effectiveness of mechanical and pharmacological prophylaxis

9.1.1 Introduction

The chapter is structured in the following way:

- a description of the different types of mechanical and pharmacological prophylaxis,
- patient views for mechanical and pharmacological prophylaxis,
- recommendations for the general use of prophylaxis methods.

Data comparing different types of mechanical and pharmacological prophylaxis for each specific population are presented in the chapters relevant to those populations.

9.1.2 Description of mechanical and pharmacological prophylaxis

9.1.2.1 Mechanical methods of prophylaxis

Venous stasis in the deep leg veins causes a decrease in the mean flow and pulsatility of the venous flow trace. Mechanical methods of DVT prophylaxis work to combat venous stasis and include:

- Anti-embolism stockings/ Graduated compression stockings (GCS)
- Intermittent pneumatic compression devices (IPCD)
- Foot impulse devices, also known as foot pumps (FID)

In the previous guideline for surgical patients[125] these three methods were combined into one 'mechanical' category as the evidence did not indicate that there was a difference in effectiveness between the devices. For this guideline, anti-embolism stockings have been separated out from the other methods on the basis that they used a passive mechanism for reducing the risk of VTE whereas the other two methods used 'active' methods. Additionally, the distinction between IPCD and FID is not always clear and therefore in this guideline, intermittent pneumatic compression devices and foot impulse devices have been combined and are treated as equally effective.

Unlike pharmacological prophylaxis, none of the mechanical methods are associated with an increased risk of bleeding.

Anti-embolism stockings / graduated compression stockings (GCS)

The term compression hosiery refers to two different products; anti-embolism stockings (AES) and graduated compression stockings (GCS). Although the terms AES and GCS are often used inter-changeably and both offer graduated compression, they have different indications, different British and European Standards and different levels of compression. AES are designed for the prevention of VTE in the immobile patient and GCS are designed for management and treatment of conditions such as venous leg ulcers and lymphoedema in the ambulant patient. This guideline covers VTE prophylaxis only and therefore any recommendations regarding compression hosiery refer to AES only. Within this guideline we have used the abbreviation "GCS" to cover both antiembolism stockings and graduated compression stockings.

Anti-embolism stockings exert graded circumferential pressure from distal to proximal regions of the leg. They have two potential actions in preventing DVT in the immobile patient exerting graduated compression increases blood flow velocity and promotes venous return, and preventing passive venous distension is thought to prevent sub-endothelial tears and the activation of clotting factors. Application of AES is not without risk, it is important that patients are fully assessed and their legs carefully measured before stockings are fitted and that stocking use is closely monitored.

The Sigel profile which equates to a graduated compression pressure profile of 18mmHg at the ankle, 14mmHg at the mid calf, 8mmHg at the Knee (popliteal break), 10mmHg at the lower thigh and 8mmHg at the upper thigh was found to increase deep venous flow velocity by 75%600. The current British and European Standards for AES [BS7672 (1); ENV 12719(70)] do not replicate the Sigel profile and the British Standard only requires pressure to be measured at three points rather than the five specified by Sigel. Healthcare professionals must consider the clinical evidence available for each individual product when purchasing and prescribing AES.

Anti-embolism stockings are contraindicated in patients with peripheral arterial disease, arteriosclerosis, severe peripheral neuropathy, massive leg oedema or pulmonary oedema, oedema secondary to congestive cardiac failure, local skin/soft tissue diseases such as recent skin graft or dermatitis, extreme deformity of the leg, gangrenous limb and doppler pressure index < 0.8, or cellulitis.

The length of stockings is a controversial issue and there is no clear randomised evidence that one length of stocking is more effective than another. Thigh length stockings can be more difficult to fit and often roll down creating a tourniquet effect. Clinical judgement, patient preference, concordance and surgical site are all important issues when deciding on stocking length.

Intermittent pneumatic compression (IPCD) devices

IPCD involves the use of inflatable garments wrapped around the legs, which are inflated by a pneumatic pump. The pump provides intermittent cycles of compressed air which alternately inflate and deflate the chamber garments, enhancing venous return.[61] It combats VTE through its haemodynamic effect on reducing venous stasis and by stimulating fibrinolytic activity.[182] This fibrinolytic mechanism is involved in the dissolution of clot and prevention of thrombus formation.[109]

Foot impulse devices (FID)

Foot impulse devices (or foot pumps) increase venous outflow and reduce stasis in immobilized patients. The haemodynamic effect of the pumping mechanism in the sole of the foot is activated by weight bearing.[56] On weight bearing the venous plexus in the sole is rapidly emptied into the deep veins of the legs. The pulsatile flow produced by walking reduces the risk of thrombus formation. It is within this physiological mechanism that the foot impulse device is designed to stimulate the venous pump artificially by compressing the venous plexus and mimicking normal walking and reducing stasis in immobilised patients.

9.1.2.2 Pharmacological prophylaxis

Fondaparinux

Fondaparinux is a synthetic pentasaccharide, which is based on the antithrombin binding region of heparin in the body. It acts by potentiating the antithrombin (ATIII) inhibition of factor Xa. However, it does not directly inhibit thrombin, because this requires a minimum of 13 additional saccharide units which is present in unfractionated heparin and low molecular weight heparin. It is therefore a

specific, indirect inhibitor of activated factor Xa through its potentiation of antithrombin. It is given subcutaneously postoperatively and administered once daily.

Heparins

Natural heparin is a mixture of mucopolysaccharides of differing chain lengths and hence molecular sizes. Such 'unfractionated' pharmaceutical heparin (UFH) consists of chains of molecular weights from 5000 to over 40,000 Da (average 20,000 Da). Heparin acts as an anticoagulant by binding and accelerating the action of antithrombin, a naturally occurring inhibitor of thrombin and other coagulation enzymes (X, IX, XI and XII).

By distinctly different processes of fractionating or depolymerisation of natural heparin, several preparations of low molecular weight heparins (LMWH) are produced. Thus, although they are dissimilar in physical, chemical and biological properties, they consist of short chains of polysaccharides with an average molecular weight 3000 Da. They bind less avidly to other heparin binding proteins in the blood and are therefore more biologically available at lower doses and have more predictable levels. Both unfractionated and low molecular weight heparins can be administered intravenously (boluses and continuous) or by subcutaneous injections (twice to three times for UFH, once to twice daily for LMWH).

In addition to the outcomes for venous thromboembolism and major bleeding, we also considered heparin-induced thrombocytopenia (HIT). Few trials reported this is outcome, we have reported it when available.

Vitamin K antagonists

Warfarin is a coumarin derivative and acts as a vitamin K antagonist.

The synthesis of active clotting factors II, VII, IX and X (as well as the anticoagulant proteins C and S) requires carboxylation of glutamic acid residues which is dependent on the presence of vitamin K. Antagonism of vitamin K therefore reduces the amount of these factors, thereby producing a state of anticoagulation.

Warfarin is usually given at an adjusted, variable doses to achieve a therapeutic level, as estimated by attaining an INR (International Normalised Ratio) of 2.5. This requires frequent monitoring and takes approximately 5 days for a stable antithrombotic effect to be achieved. There is much variability in responses to warfarin, which is determined by several factors including age, genetic status, medications, diet and medical conditions. The most important complication of anticoagulation is bleeding but, if required, the effect of warfarin can be reversed with vitamin K, prothrombin concentrates and replenishment of clotting factors by the use of fresh frozen plasma.

Aspirin

Aspirin inhibits platelet function through its irreversible inhibition of the enzyme cyclooxygenase- 1 (COX-1) and thereby blocking thromboxane A2 production. Thromboxane induces platelet aggregation (and vessel wall vasoconstriction) which are required for the clotting cascade and thrombus formation. This effect lasts for the duration of the platelet lifespan. However, although it may take 10 days for the entire platelet population to be renewed, haemostasis has been shown to be normal if 20% of them have normal COX activity. The Guideline Development Group separated studies of aspirin into two categories; those using 'high dose' aspirin (classified as 300mg per day or more) or 'low dose' aspirin (classified as less than 300mg per day).

Dabigatran

Dabigatran etexilate is a new oral anticoagulant that has been licensed during the development of the guideline. It is direct inhibitor of the enzyme thrombin. Thrombin is a key enzyme in blood clot (thrombus) formation because it enables the conversion of fibrinogen to fibrin during the coagulation cascade. Dabigatran was reviewed and approved for use for the prevention of venous thromboembolism after hip or knee replacement surgery in adults in a NICE technology appraisal published in September 2008. [127]

Rivaroxaban

Rivaroxaban is a new oral anticoagulant that has been licensed during the development of the guideline. It directly inhibits activated factor X (factor Xa). Inhibiting factor Xa interrupts the pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban was reviewed and approved for use for the prevention of venous thromboembolism after total hip or total knee replacement in a NICE technology appraisal published in April 2009. [129]

9.1.3 Patient views of and adherence to prophylaxis

9.1.3.1 Patient views and adherence to mechanical devices

Anti-embolic stockings / graduated compression stockings

We identified one study of anti-embolic stockings in orthopaedic patients[43] and two in mixed surgical patients.[12, 111, 149]

The first study was a RCT was conducted to investigate the effect of graduated compression stockings on venous haemodynamics[43]. In total, 160 patients were randomised to thigh-length or knee-length stockings. After 1 hour of wear, significantly more patients in the thigh-length group had wrinkles in their stockings (17.5% vs 7.5%) and reported discomfort (21% vs 11%). About half of the patients in each group were unable to manage the stockings independently (appendix H.6).

The second study was carried out in a London hospital with a policy of wearing thigh-length graduated compression stockings.[12, 149] A survey (observation) was carried out in 16 mixed-specialty surgical wards over one day. Ninety-nine (46%) of the 218 patients observed were wearing stockings. Of these, more patients wore knee-length stockings correctly (77 out of 85, 91%) compared with thigh-length stockings (9 out of 14, 64%). Overall, 39% (86 patients) wore a graduated compression stockings in a correct manner (appendix H.6).

The third study was a telephone interview of 12 patients who had worn anti-embolic stockings for at least 48 hours to investigate what type of information should go into a patient information leaflet on stockings.[111] The study found that patients did not receive enough information to support proper use of anti-embolic stockings (appendix H.6). More information about the findings of this study and the provision of patient information in general is presented in chapter 8.

Intermittent pneumatic compression devices(IPCD)

Four studies on patient adherence to IPCD were found. [69, 122, 142, 181] The adherence results of these studies are summarised in Table 66:   **Adherence to pharmacological, mechanical and combination prophylaxis**.

One study examined patient views on a new IPCD applied to either the calf or foot of 30 patients having elective joint replacement (appendix H.6).[185] Twenty three of the 27 patients who gave

feedback found the device either 'comfortable' or 'very comfortable'. Three patients who had reported discomfort or sleep disturbance had been allocated to the foot garment.

Foot impulse devices (FID)

Five studies reported the acceptability or/and adherence to FID with all studies conducted in hip and/or knee arthroscopy patients (appendix H.6).[7, 29, 155, 163, 198] The results of the study are summarised in Table 65.

Generally, all the studies found patients were comfortable with the FIDs. Reasons for non-adherence were discomfort around the ankles and sleep disturbances (30% and 70% respectively among patients who discontinued use) in Pitto et al.[155] Robertson et al[163] reported that pain, forceful pulsation, a tight fit and blisters were reasons for non-adherence. For more information about adherence, see Table 66: **Adherence to pharmacological, mechanical and combination prophylaxis**.

Table 65:   Summary of tables which reported patient views of foot impulse devices (FIDs)

Study	Pitto 2008 [155]	Chan 2007 [29]	Anand 2007 [7]	Robertson 2000 [163]	Westrich 2003 [198]
Population	Total knee or hip replacement				Total knee replacement
Sample size	800	30	43	120	100
Setting	NZ	Ireland	UK	US	US
Painful	0.4%		14.0%		
Affects sleep	8.8%	56.7%	27.9%		
Noise	-	26.7%	-		
Too hot	-	43.3%	-		
Restrict mobility	-	-	65.1%		
Uncomfortable	2.5%	30.0%			
Comfortable	63.1%(a)	7.1 (b)	51.2% (a)/ (7.3) (b)	55% (a)	Foot wrap 7.4 (b) Pumping action 6.1 (b)
Soothing/Relaxing	26.5%	-	53.5%		

(a) *Percentage of patients who reported the devices as comfortable.*
(b) *Mean scores from questions on comfort. Higher values represent higher comfort. Visual analogues scales (VAS) or Likert items were used. The format and definitions of response choices differ between studies. One study[29] used scales ranging from 1 to 10. Another[7] used a scale ranging from 0 to 10,*

where a score of 0 was "most uncomfortable" and 10 was "most comfortable". The third study had questions with response choices ranging from 1 to 9. [198] *(appendix H.6)*

Combination of mechanical prophylaxis methods

One observational study was found that investigated the adherence to IPCD and GCS (appendix H.6).[21] Patients were recruited based on GCS and IPCD orders from the pharmacy records. The paper does not indicate how many patients should receive both methods. The number of patients who used each of these methods correctly was reported but the total number of people who used both correctly was not reported. This paper, found no correlation between gender and adherence rates, but older patients were more likely to wear GCS or IPCD (Pearson r=0.25, p<0.01).

9.1.3.2 Patient views and adherence to pharmacological prophylaxis

Five studies which reported patient views or adherence were found and included.[30, 37, 86, 138, 178] One is a qualitative study conducted to understand patient perception of LMWH prophylaxis.[138] The other four studies looked at self-injection of LMWH in orthopaedic patients; including hip or knee replacement[37], knee replacement[178], spinal cord injury[30] (appendix H.6). Information about adherence to self-injection in patients with lower limb plaster casts were also extracted from an RCT[86] reviewed for effectiveness of intervention and presented in Table 66**: Adherence to pharmacological, mechanical and combination prophylaxis**.

The qualitative study was conducted among 28 cancer patients receiving palliative care in the UK with all patients having received LMWH for at least 5 days. [138] Recruitment continued until theme saturation was achieved. The study found that patients were aware of the purpose of subcutaneous LMWH thromboprophylaxis, and they understood that death could be a consequence of VTE. The potential benefit of reducing the risk of VTE was balanced against potential side effects (bruising was quoted) and patients found it acceptable to receive the LMWH injections (appendix H.6).

Colwell et al[37] evaluated postoperative self injection of subcutaneous LMWH injection for 21 days in 51 total hip or knee replacement patients. Patients were given routine instructions and a demonstration by the staff nurses. Written and video instructional materials were also given on discharge. Most patients (86%) performed self-injections with 14% being assisted by a family or friend. Follow up telephone interviews were conducted once per week and each patient was given a self-report diary to complete. Forty patients completed the trial, and their diaries showed that 55%, 37.5% and 7.5% had "full", "partial" and "noncompliance" to the injection regimen respectively (appendix H.6). Most patients (98%) understood the importance of self administering heparin and 68% (34/ 50) felt comfortable doing it. Generally, patients were happy with the level of information received regarding self-injection and felt that the syringe was relatively easy to use. Sixteen reported mild burning or stinging at the injection site and one reported mild bruising. The authors thought that adherence might be higher in this study than in a normal practice due to the weekly phone calls to check how patients were coping.

Spahn et al[178] evaluated postoperative self-injection of LMWH for around 10 days in knee replacement patients. Patients were provided with training for self-injection and were free to choose between self-administration or a nursing service. Assessment was carried out by anonymous questionnaire. Fully completed questionnaires were received from 69% of patients (207/300). Sixteen percent (16%, 31/191) of patients who selected self-administration of injections required family or friends to help. Only 77.3% (160/207) performed self-injection independently while 7.7% (16/207) used the nursing service. Fewer patients who self-injected independently found it 'very

unpleasant' compared to patients who engaged the help of family members or the nursing service. Overall, adherence was incomplete in 28.3% (54/191) of patients who self injected or required family or friends to help. Some injections were left out by 17.8% (34/191) of patients injections and 13.1 % (25/191) discontinued the injections early. All patients under 20 years old had incomplete adherence (N=24) compared to 18% (30/167) (p<0.001, Chi square test) among patients aged 20 years and above. (appendix H.6).

The study among patients with spinal cord injury was conducted as an RCT comparing two compounds which required once vs twice daily injections per day.[30] There were no significant differences between the two groups in terms of adherence, pain and perception of hassle of injections. The two groups were combined in analysis. On average, the patients in this did not find the injections painful (mean1.5 (s.d. =0.61) and the range of scores chosen by patients were 1-4 (1=not painful at all, 10=extremely painful). When asked to compare the hassle of injections to taking pills three times a day, the mean score was 2.5 (s.d.= 2.16), and the range of scores chosen by patients was 1 to 10 (1=much less of a hassle, 10= very much of a hassle). The adherence data from this study are shown in Table 66: **Adherence to pharmacological, mechanical and combination prophylaxis**.

9.1.3.3 Comparison of patient views and preferences of different types of interventions

Comparison of different types of mechanical devices

We identified two studies that compared mechanical interventions(appendix H.6).[163, 203] In one study, IPCD plus anti-embolism / graduated compression stockings (GCS) (n=104) were compared with FIDs (n=120) in hip joint replacement patients.[163] Significantly more patients were "comfortable" or had no complaints with the FID (71% vs. 55% in IPCD plus GCS group). Thirty-five participants in the foot impulse device group were having revision surgery and had previously used an IPCD. Of these, 69% preferred the FID, 20% preferred the IPCD and 11% had no preference (appendix H.6).

The second study[203] was an RCT that compared the use of pneumatic foot wraps (Plexi-Pulse) with IPCD in adults undergoing major spinal procedures. All participants also wore thigh-length GCS. The devices were started postoperatively and worn when in bed until discharge. There was a wide range of responses in both groups ranging from extremely comfortable to extremely uncomfortable. There was no difference in visual analogue scores for comfort between the two groups (appendix H.6).

Comparison of different types of pharmacological prophylaxis

No studies comparing different types of pharmacological prophylaxis were found.

Comparison of different mechanical and pharmacological prophylaxis

We found two studies comparing patient views for mechanical interventions with those for pharmacological interventions (Evidence Table H.6, appendix H).[7, 110]

One study looked at the views of 207 women undergoing surgery for gynaecological malignancy who were randomised to LMWH or IPCD in an RCT.[110] Fewer patients (4%) receiving LMWH reported discomfort or side effects compared to the IPCD group (26%) who experienced discomfort, inconvenience, problems and/or side effects. The most common side effect associated with the IPCD

was excessive perspiration. Eleven percent indicated that they removed the IPCD when the nurse was out of the room. The IPCD was not optimally functional in 9.6% patients at some point of postoperative recovery period whereas the protocol for LMWH was not strictly adhered to in 6.8% patients. Overall, there were no significant differences in preference or adherence between the two groups using although IPCD appear to lead to more discomfort (appendix H.6).

A UK study compared the acceptability of FID to subcutaneous LMWH injections among patients who had total hip or knee replacements and received both these prophylactic methods.[7] Patient ratings for comfort and pain were slightly better (not significant) for the FID, (mean score of comfort level was 6.3 for LMWH and 7.3 for FID, 10= most comfortable; 14% found LMWH painful vs. 11.6% for FID). However, significantly more patients answered that they "would rather not have these" for FID (37%) compared to LMWH (14.0%) and willingness to continue the prophylaxis method for 4 weeks was higher for LMWH (76.7% vs. 51.2% in FID) (appendix H.6).

Discussion on Patient views

Adherence rates obtained from studies using various thromboprophylaxis methods are tabulated in Table 66: **Adherence to pharmacological, mechanical and combination prophylaxis**.

Across the studies, there were no consistent definitions of adherence and methods of measurements used. The setting of the studies (e.g. RCTs vs observational studies, different types of wards) and methods of reporting adherence could have contributed to differences identified. In general, adherence for subcutaneous LMWH injection during hospitalisation reached more than 99%, both for once and twice daily injections.[30] However, 12 % dropped out from a post-discharge RCT due to discomfort or refusal to self-inject.[86] Adherence to FIDs ranged from 30% to 95%, depending on the timing of observations and definition of adherence used. Similarly, adherence to GCS and IPCD varies depending on definition of adherence.

Table 66: Adherence to pharmacological, mechanical and combination prophylaxis.

Study	Population & setting	Methods and definition of measurement	Outcomes (Adherence)
Pharmacological			
SC LMWH (in hospital) [30]	Spinal cord injury (United States)	Adherence with injections as recorded in hospital logs	▪ 99.2% for twice daily ▪ 99.5% for once daily regimen
SC LMWH (self administered) [86]	Below knee plaster cast, N=148 RCT (Denmark)	Number of patients who stayed in trial (no discomfort with self injection)	▪ 88% continued with trial ▪ 60% reported no problems administering self-injection
SC LMWH (self-administered) [178]	TKR N=191 self-injection patients from 300 recruited. (Germany)	Self-reported (questionnaire, interview). Incomplete adherence include early termination or missed doses	▪ 71.7% (137/191) overall ▪ 0% in subgroup of patients under 20 years
SC LMWH (self-administered) [37]	THR/TKR N=51, 40 evaluable Observational (United States)	Self-completed diaries reporting adherence for 21 days.	▪ 55% full adherence, 37.5% partial adherence, 7.5% non-adherence
Mechanical – foot impulse devices (FID)			
FID [163]	THR/TKR, N=104 Observational study (United States)	Total number of hours worn, as measured by the internal measurement device of the FID and hourly nursing observation (b)	▪ 72 % (52/72 hours for 3 days post operatively
FID [198]	TKR, N=100 Observational (United States)	As charted by around clock, hourly observations by clinical staff.	▪ 87.1% overall compliance
FID [29]	THR/TKR, N=30 Observational study (Ireland)	Reported as % of adherent observations per day (3 random observations per day conducted).	▪ Day 3 post surgery: 80-90% ▪ Day 5 post surgery: 30%
FID [7]	THR/TKR, N=43 Observational study (UK)	Number of patients who discontinued foot pump due to pain	▪ 95.3% (41/43)

FID+/- GCS[154]	THR/TKR, N=846 RCT study (New Zealand)	1) Internal measurement device of the FID 2) Discontinuation Protocol requires patients to use 16 hours per day	1) 66% (15.9/24 hours) 2) 95 % (800/846) discontinuation
Mechanical – IPCD			
IPCD (thigh-length) [69]	THR, N pre/post intervention(a) = 49/30 Observational (Vancouver)	Monitoring device (external) % time used	• Pre-intervention: 78±17% • Post-intervention: 80.6±14.0%
IPCD (non portable vs portable devices) [122]	Trauma, N=33 Observational (US)	Monitoring device Overall % of time used	• 58.8% for non portable devices; 77.7% for portable devices
IPCD (length not specified) [181]	Surg (including ICU) N unknown Observational (California)	Reported as % of correct usage observations (once in the morning & once in the evening). Pre and post education imitative	• Surgical ward: Pre: 62% (131/213) Post: 65% (93/142) • Non-surgical ward: Pre & post: 48% (73/152)
IPCD (calf length) [142]	Orthopaedic (trauma/THR/TKR) N=70 Observational (Pennsylvania)	Surveys (Patients at Day 3/ discharge, staff at end of study) % time used	• 81-85% patient reported • 66-71% staff reported
Mechanical - GCS			
GCS [12, 149]	Mixed surgery wards N=218 Observational (UK)	Number of patients observed to wear stockings and wearing it correctly. Observation carried out in 16 wards in 1 day.	• 9/14 thigh-length • 77/85 knee-length • Overall correct use: 86/218 (39%)
Mechanical – GCS + IPCD or FID			
GCS + IPCD [163]	THR/TKR Observational N=120	Hourly nursing observation (b)	• Total of 64.1 hours • 75.4% (54.3/72 hours) for 3 days post operatively
GCS + IPCD [21] 60% and 51% had thigh-length IPCD respectively	Med & surg, N=137 Observational (California)	% wearing IPCD or GCS, and % of correct fitting observed at one time point (timing not stated)	• IPCD: 29.2% wearing, 19% wearing correctly • GCS: 62.8% wearing, 25.5% wearing correctly

THR = Total hip replacement; TKR = Total knee replacement; N = number of participants, GCS = anti-embolism stockings/ graduated compression stockings; IPCD – Intermittent pneumatic compression devices; SC = subcutaneous

For details about the studies, see (appendix H.6).

    (a) *In this study, adherences were measured pre and post an awareness campaign among staff and provision of a small leaflet to patients to remind them about keeping the devices on.*

    (b) *The methods of adherence measurement in for the FID and IPCD+GCS arms for this study was different because the FID had an integral measurement meter. The IPCD+GCS combination had to be done only through hourly observations by nursing staff.*

9.1.4 Recommendations and link to evidence – mechanical prophylaxis

The following recommendations cover the general use of mechanical methods of prophylaxis. Recommendations for specific patient groups are discussed in the later chapters.

Recommendation	**1.3.1 Do not offer anti-embolism stockings to people who have:** • **suspected or proven peripheral arterial disease** • **peripheral arterial bypass grafting** • **peripheral neuropathy or other causes of sensory impairment** • **any local conditions in which anti-embolism stockings may cause damage – for example, fragile 'tissue paper' skin, dermatitis, gangrene or recent skin graft** • **known allergy to material of manufacture** • **severe leg oedema** • **major limb deformity or unusual leg size or shape preventing correct fit.** **Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds. [2010, amended 2018]**
Trade off between clinical benefit and harms	In cases where patients have a known contra-indication to anti-embolism stockings this outweighs the benefit of reducing the risk of VTE and the stockings should not be offered. The patient should be offered alternative methods of prophylaxis.
Economic considerations	None
Other considerations	None

Recommendation	**1.3.2 Ensure that people who need anti-embolism stockings have their legs measured and that they are provided with the correct size of stocking. Anti-embolism stockings should be fitted and patients shown how to use them by staff trained in their use. [2010]**
Recommendation	**1.3.3 Ensure that people who develop oedema or postoperative swelling have their legs re-measured and anti-embolism stockings refitted. [2010]**
Trade off between clinical benefit and harms	Stockings protect against venous thrombosis but if incorrectly fitted the harms may outweigh the benefits. Poorly fitted stockings or those of an incorrect shape and size have the potential to cause a tourniquet effect on the proximal part of the limb where the stocking is applied. This can result in ischaemia and an increased risk of thrombosis development.
Economic considerations	Although there is a cost involved in the nursing time required to fit stockings clearly it would not be cost effective to provide stockings that were not effective at reducing the risk of VTE.
Other considerations	Properly fitting stockings increase the effectiveness at reducing VTE. Poorly fitting stockings are unlikely to be worn by patients. Patients legs may swell during hospitalisation, particularly after surgery and so it is important that patients legs are re-measured in this situation.

Recommendation	**1.3.4 If arterial disease is suspected, seek expert opinion before fitting anti-embolism stockings. [2010]**
Trade off between clinical benefit and harms	Although it takes staff time to measure pedal pulses the committee considered that this was worthwhile in certain high risk patients as it is important to ensure the safety of patients wearing anti-embolism stockings.
Economic considerations	It is clear that the cost-effectiveness of stockings is dependent on patient selection, information and adherence. In our cost-effectiveness analyses comparing different types of prophylaxis we included the cost of clinician time for the administration of anti-embolism stockings.
Other considerations	None

Recommendation	**1.3.5 Use anti-embolism stockings that provide graduated compression and produce a calf pressure of 14-15 mmHg. (This relates to a pressure of 14–18 mmHg at the ankle and is in line with British Standards 6612:1985 Specification for graduated compression hosiery and 7672:1993 Specification for compression, stiffness and labelling of anti-embolism hosiery.) [2010]**
Trade off between clinical benefit and harms	The effectiveness of these prophylactic methods in reducing the risk of pulmonary embolism and deep vein thrombosis was considered against the potential of causing bleeding problems. The correct pressure profile needs to be used to give the best balance between benefits and harms.
Economic considerations	None
Other considerations	The above pressure profile has been identified as the profile which is effective at reducing the risk of venous thromboembolism

Recommendation	**1.3.6 Encourage people to wear their anti-embolism stockings day and night until they no longer have significantly reduced mobility. [2010]**
Recommendation	**1.3.7 Remove anti-embolism stockings daily for hygiene purposes and to inspect skin condition. In people with a significant reduction in mobility, poor skin integrity or any sensory loss, inspect the skin 2 or 3 times a day, particularly over the heels and bony prominences. [2010]**
Relative values of different outcomes	The committee considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as PTS. However the safety of the patient and adverse effects of the prophylaxis should be considered.
Economic considerations	The cost-effectiveness of stockings will continue as long as the patient is immobile. However, they may no longer be cost-effective when the patient has returned to the community because of the need to monitor use. There is no cost-effectiveness evidence for the prophylactic use of stockings beyond discharge.
Other considerations	None

Recommendation	**1.3.8 Monitor the use of anti-embolism stockings and offer assistance if they are not being worn correctly. [2010]**
Trade off between clinical benefit and harms	Not wearing the stockings as instructed may mean the patient is not adequately protected against VTE. Poorly fitted stockings or those of an incorrect shape and size have the potential to cause a tourniquet effect on the proximal part of the limb where the stocking is applied. This can result in ischaemia and an increased risk of thrombosis development.
Economic considerations	Clearly, it would not be effective or cost-effective to provide stockings, if contra-indicated. Regular checking will reduce the risk of patients experiencing adverse events caused by the use of stockings which may add additional cost to the health service.
Other considerations	None

Recommendation	**1.3.9 Stop the use of anti-embolism stockings if there is marking, blistering or discolouration of the skin, particularly over the heels and bony prominences, or if the person experiences pain or discomfort. If suitable, offer intermittent pneumatic compression as an alternative. [2010, amended 2018]**
Trade off between clinical benefit and harms	The effectiveness of these prophylactic methods in reducing the risk pulmonary embolism and deep vein thrombosis was considered against the potential of causing harm and patient comfort.
Economic considerations	Clearly, it would not be effective or cost-effective to provide stockings, if contra-indicated. Regular checking will reduce the risk of patients experiencing adverse events caused by the use of stockings which may add additional cost to the health service.
Other considerations	None

Recommendation	1.3.10 Do not offer intermittent pneumatic compression to people with a known allergy to the material of manufacture. [2010, amended 2018]
Trade off between clinical benefit and harms	In cases where patients have a known contra-indication to intermittent pneumatic compression devices and foot impulse devices this outweighs the benefit of reducing the risk of VTE and these devices should not be offered. The patient should be offered alternative methods of prophylaxis.
Economic considerations	Clearly, it would not be effective or cost-effective to provide intermittent pneumatic compression devices or foot impulse devices, if contraindicated.
Other considerations	None

Recommendation	1.3.11 Advise the person to wear their device for as much time as possible. [2010, amended 2018]
Trade off between clinical benefit and harms	Not wearing the using the devices as instructed may mean the patient is not adequately protected against VTE.
Economic considerations	The cost-effectiveness of intermittent pneumatic compression or foot impulse devices will continue as long as the patient is immobile.
Other considerations	None

9.1.5 Recommendations and link to evidence – pharmacological prophylaxis

Recommendations	1.3.12 For pharmacological VTE prophylaxis in people under 18 follow the recommendations on apixaban, dabigatran etexilate, fondaparinux sodium, LMWH and rivaroxaban in this guideline. At the time of publication (March 2018) these drugs did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. [2018]
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (up to 7–90 days from hospital discharge), pulmonary embolism (up to 7–90 days from hospital discharge), fatal PE (7–90 days from hospital discharge), and major bleeding (up to 45 days from hospital discharge) as critical outcomes. The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), heparin-induced thrombocytopenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	The evidence reviewed ranged from high to very low quality and is presented in the reviews by population. All the evidence relates to people over 18 years of age however the committee view the evidence is directly applicable to those under the age of 18.
Trade-off between clinical benefits and harms	The committee discussed the importance of all people being risk assessed and offered prophylaxis according to their condition. They discussed the lack of evidence of effectiveness of prophylaxis in this age group. Despite this they are of the opinion that some people aged 16-18 are at risk of VTE. Risk assessment would determine if an individual requires prophylaxis. If shown to be at increased risk then prophylaxis should be offered according to their condition. The committee did not believe that age alone is the only risk factor for this group, for example girls in this age group may be taking a contraceptive pill. The other factors commonly associated with risk of VTE in adults could also increase the risk of VTE in under 18s. None of the methods of pharmacological prophylaxis are licenced for use in this age group. In the absence of licenced medications the committee recommend that the prophylaxis methods used for adults are used 'off-label' for young people aged 16 to 18 years old.
Trade-off between net clinical effects and costs	No economic evidence was identified in this age group. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee for consideration in each review by population (see Appendix Q). The committee acknowledged that in absence of economic and clinical evidence in those aged 16 - 18, the use of these prophylaxis strategies in this age group should be guided by the outcome of the risk assessment. The committee agreed that those considered at high risk of VTE are likely to represent a small percentage of all those aged 16-18 in the populations covered by this guideline. Hence, the cost impact is unlikely to be substantial. They also agreed that, when prescribed, the cost of the prophylaxis is likely to be off-set by the cost saved from the reduced VTE events.

Other considerations	None

All surgery

Recommendation	**1.3.13 Advise people to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods. [2010]**
Relative values of different outcomes	The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The increased risk of VTE through use of oestrogen containing oral contraceptives and hormone replacement therapy was considered.
Economic considerations	No cost effectiveness model was completed to identify the cost effectiveness of stopping these treatments before surgery. The guideline development group felt that the benefits in terms of reducing the risk of VTE after surgery may, in some patients, outweigh the benefits of maintaining therapy, and so felt that it should be considered for all relevant patients.
Quality of evidence	The systematic reviews of risk factors for VTE identified oestrogen containing oral contraceptives and hormone replacement therapy as factors which significantly increased the risk of VTE.[53, 90] These treatments although improve the quality of the patient's life are unlikely to be life threatening if stopped. Therefore consideration should be given to their continued use.
Other considerations	This recommendation is based on the recommendation from the previous surgical guideline. The Guideline Development Group used both the evidence from systematic reviews and advice provided in the BNF[85], which included the advice of when to stop these hormone treatments before elective surgery (4-6 weeks).
	Additional guidance can be found in the RCOG guidelines on guidance on venous thromboembolism and hormonal contraceptives[166] and hormonal replacement therapy and venous thromboembolism[167], and the BNF.[85]

10 Nursing care: Early mobilisation and hydration

10.1 Early mobilisation and leg exercises

10.1.1 Introduction

Immobility and lack of exercise are widely accepted as risk factors for developing venous thromboembolism. When normal venous pump function is lost as a result of bed rest, venous stasis manifests itself in two ways. Firstly, there is a decrease in the linear velocity of blood, affecting venous return from the lower extremities. Secondly, this decrease in the mean flow and pulsavity of the venous flow is followed by dilatation of the vein delaying further venous return and leading to venous stasis.

It has long been suggested that early mobilisation prevents stasis and reduces subsequent risk of thrombi formation.[93, 194] Although there are no robust clinical data or RCTs, attesting to support the value of early mobilisation in combating venous stasis, experimental physiology has demonstrated that it promotes venous return and thus reduces the risk of VTE.[56, 177]

Leg exercises are a safe and effective method of increasing venous return to the heart. The contraction during leg exercises, particularly the calf muscle pump, compresses the deep leg veins and with the aid of the venous valves, moves blood flow toward the heart. Mechanical devices that perform continuous passive motion imitate these contractions and increase the volume and velocity of venous flow.

10.1.2 Clinical evidence

We identified no RCTs that looked at the effect of early mobilisation or leg exercises on venous thromboembolism outcomes measured using objective criteria.

10.1.3 Economic evidence

We did not find any relevant economic evidence.

10.1.4 Patient views

We did not identify any patient views evidence for leg exercises or early mobilisation.

10.2 Hydration

10.2.1 Introduction

It is believed that dehydration predisposes to venous thromboembolism. Kelly et al found a strong association between dehydration after acute ischaemic stroke and VTE.[89] Allowing a patient to become dehydrated during surgery may also be associated with VTE.

10.2.2 Clinical evidence

We found one RCT that looked at the effect of intravenous saline administration on post-operative deep vein thrombosis (appendix H.7.2).[83] Sixty patients undergoing routine abdominal surgery were randomised. Thirty patients received 1 litre of Hartmann's solution per hour of surgery, and then 2-3 litres of dextrose-saline per 24 hours for 2 days. Patients in the second group were given no intravenous fluids either during or after the surgery, but small, increasing amounts of water were allowed by mouth from the first day onwards. The study did not report location of thrombosis, pulmonary embolism or major bleeding events.

Effect on DVT: Intravenous saline was associated with a significantly higher number of DVT events (RR=4.50, 95% CI 1.06-19.11, one study) (Figure 42, appendix L.7.2).

10.2.3 Economic evidence

We did not find any relevant economic evidence.

10.2.4 Patient views

We did not identify any patient views evidence for hydration.

10.3 Recommendations and link to evidence

Recommendation	**1.3.14 Encourage people to mobilise as soon as possible. [2010]**
Relative values of different outcomes	The committee considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as Post thrombotic syndrome. However the safety of the patient and adverse effects of the prophylaxis should be considered.
Trade off between clinical benefit and harms	Whilst encouraging patients to mobilise as soon as possible requires staff resources, the benefit of reducing the risk of VTE mean that it is good practice.
Economic considerations	There is no cost-effectiveness evidence for encouraging patients to mobilise early. The committee believe that this represents a good use of resources.
Quality of evidence	There is no RCT evidence to contradict the practices of encouraging patients to mobilise early or exercising their legs while immobile in bed.

Other considerations

None

Recommendation	1.3.15 Do not allow people to become dehydrated unless clinically indicated. [2010]
Relative values of different outcomes	The committee considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as PTS.
Trade off between clinical benefit and harms	It was considered that unless clinically indicated for other reasons the potential to increase the risk of VTE whilst dehydrated meant that it was good practice to avoid this happening.
Economic considerations	It seems likely that this is cost-effective, since the cost of the intervention is minimal.
Quality of evidence	We found no RCTs that looked at the effect of oral hydration on venous thromboembolism. This recommendation was developed through committee consensus.
Other considerations	None

11 Obesity

11.1 Introduction

Obesity is on the rise in England; the prevalence of obesity has increased by 11% between 1993 and 2014 (15% in 1993 and 26% in 2014).[72] With the increasing number of obese people in the England, there has subsequently been an increase in obese people admitted to hospitals. Estimates show obesity may as much as double a person's risk of developing hospital acquired venous thromboembolism (VTE)[42, 120] therefore the majority of obese people are likely to require prophylaxis. Current practice is to administer a higher than usual dose but this may not be necessary, especially if they have obesity-related liver disease. There is a lot of uncertainty about the optimal dose to use and the clinical and cost-effectiveness of using weight-based dose-adjustment versus fixed dose strategies. This review aims to assess if the dose of LMWH for prophylaxis needs to be adjusted in people who are obese in order to be clinically and cost-effective.

11.2 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?

For full details see review protocol in appendix A.

Table 67: PICO characteristics of review question

Population	Adults and young people (16 years and older) who are obese (BMI >30) who are: • Admitted to hospital • Discharged from hospital • Outpatients

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 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)
	*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) (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 (symptomatic and asymptomatic) (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 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 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

11.3 Clinical evidence

No relevant clinical studies comparing pharmacological prophylaxis with LMWH at a fixed dose to LMWH at a weight-adjusted dose for people who are obese were identified. See the study selection flow chart in appendix B and excluded studies list in appendix G.

11.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

11.5 Evidence statements

Clinical
No relevant clinical studies were identified.

Economic
No relevant economic evaluations were identified.

11.6   Recommendations and link to evidence

Recommendations	**No clinical recommendation.**
Research recommendation	**2. What is the clinical and cost effectiveness of weight-based dose-adjustment strategies of LMWH compared with fixed dose strategies of LMWH for preventing VTE in people who are very obese (BMI >35) who are admitted to hospital or having day procedures (including surgery and chemotherapy)?**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge), pulmonary embolism (symptomatic and asymptomatic) (up to 90 days from hospital discharge), fatal PE (up to 90 days from hospital discharge), and major bleeding (up to 45 days from hospital discharge) as critical outcomes. The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), and heparin-induced thrombocytopenia (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail explaining prioritisation of the critical outcomes.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	It was acknowledged that dose adjustment data are mainly obtained from pharmacodynamics studies which focus on surrogate outcomes such as measuring anti-Xa activity. However, there is no definitive evidence that anti-Xa levels are directly related to the risk of DVT/PE.[13] The committee recognised that dose adjustment is often used in very obese patients, however also acknowledged that there was no evidence found to support this in regards to clinical outcomes. Therefore, due to the absence of evidence the committee determined that a clinical recommendation could not be made. The committee did feel that this topic area is very important given the increasing incidence of obesity in the UK and decided that a research recommendation should be made.
Trade-off between net clinical effects and costs	No relevant economic studies were identified. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee for consideration (see appendix Q). The committee acknowledged that increasing doses would be more costly, with costs of higher doses of LMWH ranging from £2,866 per month for enoxaparin to £3,475 for tinzaparin. Given the lack of evidence to support the effectiveness and safety of these higher doses, the committee considered that the cost effectiveness of using higher doses for the obese is uncertain.
Other considerations	The committee made a high-priority research recommendation on weight-based dose-adjustment strategies; see appendix R for more details.

12 People using antiplatelet agents

12.1 Introduction

Aspirin, clopdidogrel and other thienopyridines and dipyridamole are prescribed for their antiplatelet actions. Aspirin has been shown to be beneficial to patients with arterial blood vessel disease at a dose of 75 mg daily. At this dose it has minimal anti-thrombotic effect. Even at high doses (greater than 300 mg daily) it is less efficient at reducing the risk of VTE formation than standard pharmacological methods. Clopidogrel, although prescribed predominantly for its antiplatelet effect in the treatment of acute coronary syndromes and following stent insertion, is not licensed for VTE prophylaxis as a single agent. Dipyridamole is used as an adjunct to anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. It is also licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks. There are no trials regarding its efficacy in the prophylaxis of VTE.

12.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people using antiplatelet agents at time of presentation?

For full details see review protocol in appendix C.

Table 68: PICO characteristics of review question

Population	Adults and young people (16 years and older) in people using antiplatelet agents on presentation to hospital

Intervention(s)	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:
	     o enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)
	     o 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*)
	     o 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:
	     o 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
Comparison(s)	Continuing/stopping antiplatelet agents (including single and dual agents) plus VTE prophylaxis treatment, versus continuing/stopping antiplatelet agents, 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.

12.3 Clinical evidence

No relevant clinical studies comparing the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people using antiplatelet agents at time of presentation were identified. See the study selection flow chart in appendix E and excluded studies list in appendix N.

12.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

12.5 Evidence statements

Clinical

No relevant clinical studies identified.

Economic

No relevant economic evaluations were identified.

12.6 Recommendations and link to evidence

Recommendations	**1.3.16 Consider VTE prophylaxis for people who are having antiplatelet agents for other conditions and whose risk of VTE outweighs their risk of bleeding. Take into account the risk of bleeding and of comorbidities such as arterial thrombosis.** • **If the risk of VTE outweighs the risk of bleeding, consider pharmacological VTE prophylaxis based on their condition or procedure.** • **If the risk of bleeding outweighs the risk of VTE, consider mechanical VTE prophylaxis. [2018]**

Research recommendation	None
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (7–90 days from hospital discharge), pulmonary embolism 7–90 days from hospital discharge), major bleeding (up to 45 days from hospital discharge) and fatal PE (7–90 days from hospital discharge) as critical outcomes.
	The committee considered health-related quality of life (up to 90 days from hospital discharge), clinically relevant non-major bleeding (up to 45 days from hospital discharge), heparin-induced thrombocytopenia (duration of study) and technical complications of mechanical interventions (duration of study) as important outcomes.
	Please see section 4.4.3 in the methods chapter for further detail explaining prioritisation of the critical outcomes.
Quality of the clinical evidence	No clinical evidence was identified that evaluated the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people using antiplatelet agents at time of presentation.
Trade-off between clinical benefits and harms	The committee noted that people who are attending hospital may be on antiplatelet agents. Some of these patients would be assessed to be at increased risk of VTE. The committee did not believe that antiplatelet agents alone are effective at reducing the risk of patients getting VTE. They also considered that research in this area is unlikely to be funded and that clinicians need advice on what to do. Consequently, having discussed the evidence the committee agreed to adopt the recommendations from CG92 for people who are already having antiplatelet agents when admitted to hospital as these were still deemed appropriate and in line with current practice. The committee highlighted that prophylaxis should be given "based on their condition or procedure" to sign-post to clinicians that they will need to refer to the relevant population specific prophylaxis recommendations (for example, condition: stroke, or procedure: cardiac surgery). Therefore no specific duration for prophylaxis is given due to the wide range of different scenarios this recommendation covers.
	The committee also noted that particular attention should be paid to bleeding risk in this group; adding pharmacological VTE prophylaxis to antiplatelet agents carries an extra risk of bleeding.
Trade-off between net clinical effects and costs	No relevant economic studies were identified. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee (see appendix Q). The committee acknowledged the lack of clinical and economic evidence and noted that current practice is in line with CG92 recommendation to consider additional prophylaxis in this population when the patient is assessed to be at increased risk of VTE. The choice of prophylaxis should be based on the likelihood of net benefit in terms of prevention of VTE but also avoiding the untoward effects of prophylaxis (for example major bleeding or side effects of mechanical prophylaxis).The committee agreed that unless there are individual risk factors that warrant the additional prophylaxis it is unlikely to be cost-effective.
Other considerations	The committee are also aware of British Society for Haematology guidance on Peri-operative management of anticoagulation and antiplatelet therapy published in 2016 (available from http://onlinelibrary.wiley.com/doi/10.1111/bjh.14344/full) which provides more detail on interrupting anticoagulation treatments.

13 People using anticoagulation therapy

13.1 Introduction

Some people admitted to hospital may be using anticoagulant therapy for treatment or prevention of an existing condition such as atrial fibrillation. Although anticoagulants offer a protective effect against VTE, they may need to be stopped for a procedure or treatment occurring while treating the current reason for attending hospital.

This review aims to assess the clinical effectiveness of different strategies for VTE prophylaxis for people who need to interrupt their anticoagulant therapy when admitted to hospital, having day procedures, and on discharge.

13.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) when interrupting anticoagulant therapy?

For full details see review protocol in appendix C.

Table 69:   PICO characteristics of review question

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

Intervention(s)	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:
	   o enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)
	   o 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*)
	   o 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
Comparison(s)	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) - 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.

13.3 Clinical evidence

One study was included in the review [171]; this is summarised in **Table 70** below. Evidence from this study is summarised in the clinical evidence summary below (**Table 71**). See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in Appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

Table 70:   Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Santamaría 2013 [171]	Intervention (n=98): Bridging LMWH, (bemiparin, 3500IU/day) (high dose). People discontinued the oral anticoagulation therapy (day -5 or -3), they started bridging therapy before the invasive/surgical procedure with bemaparin (3500IU/24 hour + matching placebo 12 hour afterwards, subcutaneously). The study medication was continued up to 5–6 days. Comparison (n=105): Unfractionated heparin, patients were discontinued the oral anticoagulation therapy (OAT) (day -5	n= 203 People taking VKA treatment for at least 3 months, required outpatient surgery, laparoscopy surgery or invasive procedures Age: aged 18 years or over; mean age 72 years(IQR 67-79) Male to female ratio1.64:1 Spain	All-cause mortality (90 days) Major bleeding (90 days): 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.	

Study	Intervention and comparison	Population	Outcomes	Comments
	or -3), they started blinded bridging therapy before the invasive/surgical procedure) with UFH (5000IU/12 hour, subcutaneously) The study medication was continued up to 5–6 days.	207		

Table 71:   Clinical evidence summary: LMWH (high dose; standard duration) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH	Risk difference with LMWH (95% CI)
Mortality, all-cause	177 (1 study) 90 days	MODERATE due to risk of bias	Peto OR 0 (-0.02 to 0.02)[b]	0 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)[c]
Major bleeding	177 (1 study) 90 days	LOW[a,c] due to risk of bias, imprecision	Peto OR 0.14 (0.02 to 1.04)	43 per 1000	37 fewer per 1000 (from 42 fewer to 2 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Absolute effects calculated manually in RevMan

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

13.4   Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

13.5   Evidence statements

Clinical

Moderate quality evidence from one study showed no difference for all-cause mortality between UFH and LMWH. Low quality evidence from the same study suggested a clinical benefit of LMWH over UFH with respect of major bleeding, although there was some uncertainty around this result with the confidence intervals also being consistent with no difference.

Economic

No relevant economic evaluations were identified.

13.6   Recommendations and link to evidence

Recommendations	1.3.17 Consider VTE prophylaxis for people at increased risk of VTE who are interrupting anticoagulant therapy. [2018]
Research recommendation	**None**
Relative values of different outcomes	The committee considered all-cause mortality, DVT, PE, fatal PE and major bleeding to be critical outcomes. The committee considered clinically relevant non-major bleeding, health-related quality of life, heparin-induced thrombocytopenia, technical complications of mechanical interventions, haemorrhagic stroke and embolic stroke to be important outcomes.
	Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	The evidence was of moderate to low quality. One study was identified, which reported 2 outcomes. The included study was at high risk of selection bias for all outcomes due to unclear reporting of sequence generation. The data on mortality at 90 days was of moderate quality, due to serious risk of bias. Major bleeding at 90 days was of low quality due to serious risk of bias and serious imprecision.
Trade-off between clinical benefits and harms	The committee noted that with the studies examining bridging therapy there was a clinical benefit of LMWH compared to UFH for major bleeding, and that there was no clinical difference between LMWH and UFH for all-cause mortality. The committee discussed the lack of data on DVT, PE and fatal PE and agreed that the lack of these critical outcomes limited the interpretation of the effectiveness of LMWH compared to UFH. The committee also noted that there was no evidence for mechanical prophylaxis in this group. Given the importance of people having adequate protection against VTE and taking into account lack of evidence of effectiveness the committee made a 'consider' recommendation for VTE prophylaxis. It is anticipated that clinicians will make a judgement on the requirement for prophylaxis taking into

	account individual patient factors and the reason for admission.
	The committee noted that people who are fully anticoagulated will not need additional pharmacological VTE prophylaxis and that if pharmacological VTE prophylaxis were to be added it would significantly increase the risk of bleeding. The committee also noted that there was no evidence examining the effectiveness of mechanical prophylaxis. Without any evidence the committee decided not to offer mechanical prophylaxis to patients receiving full anticoagulation therapy.
Trade-off between net clinical effects and costs	No relevant economic studies were identified. Unit costs of pharmacological and mechanical prophylaxis options were presented to the committee (see appendix Q). The committee considered the net clinical benefit of the additional pharmacological and mechanical prophylaxis against the difference in resource use between these strategies. The committee noted that the lack of data on VTE events for the comparison of LMWH and UFH, and the lack of any evidence for other prophylaxis strategies in people who are anticoagulated, limited their ability to draw a firm conclusion regarding the incremental clinical benefit of these strategies for the prevention of VTE in this population. However, based on their collective experience, the committee considered that it is unlikely that the addition of either mechanical or pharmacological prophylaxis when people are anticoagulated would be cost-effective, as the additional benefit is likely to be limited. The committee acknowledged, though, that where anticoagulation will be interrupted and the individual has risk factors for VTE it is likely that the additional cost of provision of prophylaxis would be off-set by the savings from the prevention of VTE events.
Other considerations	The committee noted that in order for a person to be fully anticoagulated on warfarin, their INR should be within the therapeutic range. The committee discussed what action to take when INR was not in the correct range and noted two options: people could be given VTE prophylaxis until in the correct range; or people could be fully anticoagulated rather than given VTE prophylaxis.
	The committee also discussed the need to restart anticoagulation if stopped and concluded it should be restarted as soon as possible. They also noted clinicians would need to ensure therapeutic levels of warfarin are reached or bridging is arranged post-discharge until the INR is therapeutic with appropriate arrangements for follow up for the monitoring of INR.
	The committee note that further guidance on the peri-operative management of patients on anticoagulation and antiplatelet therapy, including advice on when to restart their treatment, is provide in the British Society for Haematology guidance on Peri-operative management of anticoagulation and antiplatelet therapy published in 2016 (available from http://onlinelibrary.wiley.com/doi/10.1111/bjh.14344/full) which provides more detail on interrupting anticoagulation treatments.

14 People with acute coronary syndromes

14.1 Introduction

Patients diagnosed with acute coronary syndromes (ACS) are treated with anti-thrombotics. These treatments primarily consist of aspirin, clopdidogrel or other thienopyridines and heparin. The duration of each therapy varies, with aspirin often being life-long, clopidogrel in the order of 12 months and heparin for a period of three to five days post-event. Dual antiplatelet agents are also often given for a period which may be for up to a year after drug eluting coronary stent insertion. If full dose anticoagulation is stopped the protection it provides diminishes, allowing an increased risk of VTE. The VTE effectiveness of dual antiplatelet regimes remains largely unstudied in this context but will increase bleeding risk.

14.2 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 antiplatelet agents)?

For full details see review protocol in appendix C.

Table 72: PICO characteristics of review question

Population	Adults and young people (16 years and older) being treated for acute coronary syndromes with anticoagulants and/or antiplatelet agents who are: • Admitted to hospital • Having day procedures • Discharged from hospital • Outpatients post-discharge

Intervention(s)	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:
	o Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)
	o Certoparin (3000 units daily)
	o Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)
	o Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)
	o Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)
	• Vitamin K Antagonists:
	o warfarin (variable dose only)
	o acenocoumarol (all doses)
	o phenindione (all doses)
	• Fondaparinux (all doses)*
	• Apixaban (all doses)*
	• Dabigatran (all doses)*
	• Rivaroxaban (all doses)*
	• Aspirin (up to 300mg)*
	*off-label
Comparison(s)	Treatment for acute coronary syndromes (antiplatelet agents; anticoagulants; antiplatelet agents 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 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.

14.3   Clinical evidence

No relevant clinical studies comparing the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with acute coronary syndromes. See the study selection flow chart in appendix E and excluded studies list in appendix N. Seven studies that were included in CG92 were excluded from the review. Reasons for exclusion include incorrect population, incorrect intervention, incorrect study design and no relevant outcomes [20, 70, 92, 153], [15, 55, 195].

14.4   Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

14.5   Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

No relevant economic evaluations were identified.

14.6   Recommendations and link to evidence

Recommendations	**1.4.1 Be aware that people receiving anticoagulant drugs as part of their treatment for an acute coronary syndrome do not usually need VTE prophylaxis. See also recommendation 1.3.17. [2018]**
Research recommendation	**None**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (7–90 days from

	hospital discharge), pulmonary embolism (7–90 days from hospital discharge), major bleeding (up to 45 days from hospital discharge) and fatal PE (7–90 days from hospital discharge) as critical outcomes.
	The committee considered health-related quality of life (up to 90 days from hospital discharge), clinically relevant non-major bleeding (up to 45 days from hospital discharge), heparin-induced thrombocytopenia (duration of study) and technical complications of mechanical interventions (duration of study) as important outcomes.
	Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	No relevant clinical evidence identified. The committee noted that the studies that were previously included in the review were published in the 1970s/80s and that treatment for acute coronary syndromes has since changed. Based on this the committee agreed that these studies are no longer applicable and decided to exclude them.
Trade-off between clinical benefits and harms	No relevant clinical evidence was identified.
	The committee noted that people treated for acute coronary syndromes will be on anticoagulant agents to manage their condition. These agents would also act as prophylaxis against VTE. Consequently, the committee considered there is no need to offer additional pharmacological prophylaxis when these agents are being used (even though the level of anticoagulation with rivaroxaban/fondaparinux is not therapeutic). The committee also noted that some of these patients may be on dual or triple antiplatelet therapy and adding prophylaxis could increase the risk of bleeding.
	For this population of people with acute coronary syndromes, the committee decided to cross-refer to the recommendations for people using anticoagulation and people using antiplatelet agents.
	The committee also noted that there was no evidence examining the effectiveness of mechanical prophylaxis. Without any evidence the committee decided not to offer additional mechanical prophylaxis to patients taking vitamin K agonists or receiving full anticoagulation therapy.
Trade-off between net clinical effects and costs	No relevant economic studies were identified. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee (see appendix Q). The committee acknowledged that this population will be receiving therapeutic doses of anticoagulation and additional prophylaxis is unlikely to offer a clinical benefit. The committee considered the possible side effects and the additional cost of prescribing prophylaxis to this population and considered that offering additional prophylaxis to this population is unlikely to be cost effective.
Other considerations	The committee note that further guidance on the peri-operative management of patients on anticoagulation and antiplatelet therapy, including advice on when to restart their treatment, is provide in the British Society for Haematology guidance on Peri-operative management of anticoagulation and antiplatelet therapy published in 2016 (available from http://onlinelibrary.wiley.com/doi/10.1111/bjh.14344/full) which provides more detail on interrupting anticoagulation treatments.

15 Acute stroke patients

15.1 Introduction

Recent stroke has been associated with an increased risk of developing venous thromboembolism (VTE).[58] This increased risk of VTE is thought to be due to the alteration in blood flow as a results of the weakness in the affected limb, possibly leading to vessel wall injury, and a resulting hypercoagulable state related to changes in the blood after stroke.[65] Diagnosing DVT after stroke may be difficult as symptoms may be similar to those related to the stroke such as leg swelling.

Stroke is divided into two main types: ischaemic stroke caused by blood clots preventing blood flow to the brain, and haemorrhagic stroke caused by bleeding into/of the brain. Both types of stroke are associated with an increased risk of VTE.[65]

15.2 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?

For full details see review protocol in appendix C.

Table 73: PICO characteristics of review question

Population	Adults and young people (16 years and older) being treated for stroke

Intervention(s)	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 (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 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)

	o Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) o Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) • Vitamin K Antagonists: o warfarin (variable dose only) o acenocoumarol (all doses) o phenindione (all doses) • Fondaparinux (all doses)* • Apixaban (all doses)* • Dabigatran (all doses)* • Rivaroxaban (all doses)* • Aspirin (up to 300mg)* *off-label
Comparison(s)	Treatment for stroke (antiplatelet agents/warfarin) plus VTE prophylaxis treatment, versus treatment for stroke (antiplatelet agents/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) o 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.

15.3 Clinical evidence

Seventeen studies were included in this review. Fifteen studies were included in the previous guideline (CG92). [14, 31, 34, 51, 52, 78, 95, 112, 113, 121, 145, 156, 157, 170, 176]. Two studies were included in the review for the first time; [33, 48].

An addendum was completed for CG92 in June 2015, for the stroke population. This addendum identified one study that was not previously included in CG92; this study was also identified in the search and is included in this review[33].

These are summarised in **Table 74** below. Evidence from these studies is summarised in the clinical evidence summary tables below (**Table 75**, **Table 76**, **Table 77**, **Table 78**, **Table 79**, **Table 80**, **Table 81**, **Table 82**, **Table 83**, **Table 84**). See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

One of the studies that was originally included in CG92, was excluded from this review as the paper is a conference abstract; [46].

Table 74: **Summary of studies included in the review**

Study	Intervention and comparison	Population	Outcomes	Comments
Bath 2001[14]: TAIST trial	Intervention 1 (n=508): LMWH, tinzaparin, 100 IU/kg once daily (high dose) subcutaneously given for ten days Comparison (n=491): Aspirin, 300mg orally given once daily for ten days Concomitant treatment: Leg compression stockings were recommended in all patients who were not fully mobile.	n=999 People within 48 hours of an acute ischaemic stroke Age (median): 74 years Gender (male to female ratio): 1.22:1 Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Netherlands,	All-cause mortality (90 days) DVT (symptomatic and asymptomatic) (15 days): confirmed by venography or ultrasonography PE (15 days): confirmed by high-probability ventilation perfusion scan, pulmonary angiography or necropsy and death Major bleeding (15 days): defined as	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
		Norway, Sweden, UK	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. Thrombocytopenia (15 days) Modified Rankin scale (score 0-2) (90 days): measure of disability, no disability to slight disability (higher score is worse) Barthel Index (score 60-100) (90 days): measure of activities of daily living (ADL) (higher score is better)	
Dennis 2009[34]: CLOTS-1 trial	Intervention (n=1256): AES, above knee/thigh length plus routine care. AES were applied to both legs as soon as possible after randomisation, worn day and night until either the patients were independently mobile around the ward, discharged or patient refused to wear them. Comparison (n=1262): No prophylaxis plus avoidance of AES Concomitant treatment Receipt of anticoagulant (warfarin, heparin or LMWH) 30% in stocking-arm and 34% in controls.	n=2518 Newly immobile people with suspected stroke admitted to hospital, 85% ischaemic stroke Age (mean): 76 years Gender (male to female ratio): 1:1.03 55 centres in the UK, 7 in Italy and 2 in Australia	All-cause mortality (30 days) DVT (symptomatic and asymptomatic) (30 days): confirmed on a screening compression Doppler ultrasound (CDU). PE (symptomatic and asymptomatic) (30 days): confirmed by imaging or autopsy Fatal PE (30 days): confirmed by autopsy Mechanical complications – skin breaks/ulcers/blisters/ skin necrosis (30 days)	Pragmatic trial with high levels of partial-compliance with stockings (73% total compliance). Screening ultrasound also only partially complete (<56% complete for intervention arm, <60% complete for control)

Study	Intervention and comparison	Population	Outcomes	Comments
			Mechanical complications – lower limb ischaemia/amputation (30 days)	
Dennis 2010[31]: CLOTS-2 trial	Intervention (n= 1552): AES (above-knee) and routine care Comparison (n=1562): AES (below-knee) and routine care Concomitant treatment Anticoagulant use 13% in both arms. Antiplatelet use allowed.	n=3114 People with suspected stroke admitted to hospital, newly immobile 81% ischaemic stroke Age (mean): 76 years Gender (male to female ratio): 1:1.02 UK, Italy, the Republic of Ireland, Australia, Czech Republic, Portugal, India, Canada and Mexico.	All-cause mortality (30 days) DVT (symptomatic and asymptomatic) (30 days): detected by compression duplex ultrasonography or venography. PE (symptomatic and asymptomatic) (30 days): confirmed on computed tomography pulmonary angiography or ventilation-perfusion isotope scanning or autopsy Mechanical complications –skin concerns (30 days): confirmed by compression duplex ultrasonography Mechanical complications – discomfort (30 days)	
Dennis 2011[48] Clots collaboration 2013[33]	Intervention (n=1438): IPCD, sequential compression system, on both legs. Used thigh-length sleeves. Applied continuously both day and night for minimum of 30 days from randomisation or until a second screening. Stopped was once patient was mobile, discharged from hospital, declined to continue IPC. Comparison (n=1438):	n=2876 People with suspected stroke admitted to hospital, newly immobile 84% ischaemic stroke Age (mean): 74.6 years Gender (male to female ratio): 1:1.08	All-cause mortality (30 days) DVT (symptomatic and asymptomatic) (30 days): confirmed using compression duplex ultrasound PE (symptomatic and asymptomatic) (30 days): confirmed using imaging – no further details provided Mechanical complications – skin	New study. Screening ultrasound also only partially complete (<66% complete in both groups)

Study	Intervention and comparison	Population	Outcomes	Comments
	No prophylaxis. No further details reported	UK	breaks/ulcers/blisters/ skin necrosis (30 days): confirmed using imaging – no further details provided	
Diener 2006[51]	Intervention (n=272): LMWH, certoparin 3000IU antiXa once daily subcutaneously plus 2 placebo injections for 12-16 days. Started within 24 hours of stroke symptom onset. Comparison (n=273): UFH, 5000IU, 3 times daily subcutaneously for 12-16 days. Started within 24 hours of stroke symptom onset. Concomitant treatment: Anti-platelets allowed: aspirin 78% equal, aspirin + dipyridamole 11% v 18%, clopidogrel 18% equal	n=545 People within 24 hours of ischaemic stroke (n=545) Age (mean range): 66.3-67.3 years Gender (male to female ratio): 1.35:1 Multicentre, EU	All-cause mortality (90 days) PE (16 days): definition not reported Major bleeding (16 days): 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) Fatal PE (16 days): confirmed by positive D-dimer Heparin induced thrombocytopenia (timepoint: unclear): confirmed by measurements of antibodies. Neurological bleeding (7 days): CT scan performed routinely and anytime in case of clinical suspicion of intracranial haemorrhage.	Included in previous guideline. Intracranial bleeding used as indirect outcome for haemorrhagic transformation of ischaemic stroke
Duke 1983[52]	Intervention (n=35) UFH, 5000 IU subcutaneously given every 8 hours (three times daily) for seven days. Comparison (n=30):	n=65 People with partial stable stroke within 48 hours of stroke onset Age (mean): Details	DVT (symptomatic and asymptomatic) (7 days): defined by fibrinogen leg scanning	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	No prophylaxis, placebo for seven days.	not reported Gender (male to female ratio): Details not reported		
Hillbom 2002[78]	Intervention (n=106) LMWH, enoxaparin 40mg daily for 10 days. 2 placebo injections given at 8 hourly intervals. Comparison (n=106) UFH 5000 IU subcutaneously given three times a day for ten days, at 8 hourly intervals	n=112 People within 48 hours of acute ischaemic stroke and paralysis Age (mean range):68-69 years Gender (male to female ratio): 1.49:1 Multicentre, Finland	All-cause mortality (90 days) DVT (symptomatic and asymptomatic)(10 days): confirmed bilateral ascending phlebography and autopsy PE (10 days): confirmed by ventilation perfusion scan and pO2 when clinically indicated. Fatal PE (10 days): confirmed by autopsy Major bleeding (10 days): unclear definition reported Haemorrhagic transformation of ischaemic stroke (10 days): confirmed by CT scan within 24 hours of final administration	Included in CG92 Significantly more obese and diabetic in UFH group
Lacut 2005 [95]	Intervention (n=74): IPCD (length not specified) in combination with AES (length not specified) alone from as soon as participant was admitted to standard care for up to 10 days. Comparison (n=77) AES alone from as soon as participant was admitted to standard care for ten days	n=151 People with documented intracerebral haemorrhage (haemorrhagic stroke) Age (mean): 62.8 years Gender (male to female ratio): 1.4:1 France	All-cause mortality (90 days) DVT (symptomatic and asymptomatic) (12 days): confirmed by compression ultrasonography	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
McCarthy 1977[113]	Intervention (n=16): UFH, 5000IU subcutaneously given three times a day (every 8 hours) for 14 days Comparison (n=16): No prophylaxis	n=32 People within 48 hours of an acute stroke Age (mean range): 78.2-78.9 years Gender (male to female ratio): 1:1.9 UK	All-cause mortality (28 days) DVT (symptomatic and asymptomatic) (14 days): confirmed by radiofibrinogen uptake test	Included in CG92
McCarthy 1986[112]	Intervention (n=144): UFH, 5000 IU subcutaneously given three times a day (every 8 hours) for 14 days Comparison (n=161): No prophylaxis	n=305 People within 48 hours of an acute stroke % ischaemic stroke unclear. Age (mean±SD): 76 ± 8.1 years Gender (male to female ratio): 1:1.31 UK	All-cause mortality (28 days) DVT (symptomatic and asymptomatic) (14 days): confirmed by radiofibrinogen uptake test	Included in CG92
Muir 2000[121]	Intervention (n=65): AES, above-knee, for seven days Comparison (n=32): No prophylaxis Concomitant treatment: Standard care for patients included CT scanning or MRI, aspirin, IV fluids or those unable to swallow and early mobilisation within 24 hours of admission.	n=97 People within 72 hours of an acute stroke, currently unable to mobilise independently % ischaemic not given Age (mean): 76 years Gender (male to female ratio): Not reported UK	All-cause mortality (7 days) DVT (symptomatic and asymptomatic) (7 days): confirmed by Acuson 128 colour-flow Doppler ultrasound with motion discrimination software PE (symptomatic and asymptomatic) (7 days): definition not reported	Included in CG92
Pambianco 1995[145]	Intervention 1(n=120): UFH, 5000 – 10000 IU three times daily, adjusted to give PTT	n=360 People in rehabilitation up to	All-cause mortality (28 days) DVT (symptomatic and	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	30.0-39.9, for 28 days or until discharge Intervention 2 (n=117): IPCD, anti-thrombic pump (double lined stoking containing inflatable bladder, at night for 28 days Comparison: No prophylaxis (n=115) Concomitant treatment All cases received bilateral below-knee stockings	10 weeks after an ischaemic stroke who were paralysed or severely weak in lower limbs Age (mean±SD): 72.2 ± 9.5 years Gender (male to female ratio): 1:1.44 USA	asymptomatic) (28 days): screened for by: B-mode 2-dimensional imagine and pulsed Doppler ultrasound at or above the popliteal vein twice a week until the completion of the study or discharge	Not dealing with acute stroke, but during rehabilitation, therefore not pooled with other studies.
Prasad 1982[156]	Intervention (n=13): IPCD, 24h then 3h three times daily for the remaining nine days Comparison (n=13): No prophylaxis Concomitant treatment: Received potassium iodide daily as part of the trial	n=26 People within 72 hours of a stroke with weakness or paralysis on one side (hemiplegia) Age (mean range: 78-80 years Gender (male to female ratio): 1: 1.17 UK	DVT (symptomatic and asymptomatic) (10 days): screened for by daily FUT scanning	Included in CG92
Prins 1989[157]	Intervention (n=30): LMWH, dalteparin, 2500 IU, twice daily (standard dose), subcutaneously administered 14 days Comparison (n=30): Placebo, 0.9% saline, subcutaneously administered twice daily for 14 days	n=60 People within 72 hours of an acute ischaemic stroke Age (median): 76 years Gender (male to female ratio): 1:1 Netherlands	All-cause mortality (14 days) DVT (symptomatic and asymptomatic)(14 days): confirmed by fibrinogen scan and unilateral phlebography PE (14 days): definition not reported	Included in CG92
Sandset	Intervention (n=52):	n=103	All-cause mortality (14	Included in

Study	Intervention and comparison	Population	Outcomes	Comments
1990[170]	LMWH, dalteparin, 3000-5500IU once daily (depending on weight) (standard dose), subcutaneously given for 14 days or until discharge from the hospital if earlier. Comparison (n=51): No prophylaxis, 0.9% sodium chloride was subcutaneously administered for 14 days or until discharge from the hospital if earlier.	People within 72 hours of an acute ischaemic stroke Age (mean): 75 years Gender (male to female ratio): 1:1 Norway	days) DVT (symptomatic and asymptomatic) (14 days): confirmed by venography and B-mode ultrasound scanning Major bleeding (12 days): defined as a fall in haemoglobin level of more than 20gm/litre, or led to blood transfusion, or was intracranial or fatal. Fatal PE (14 days): confirmed by autopsy Haemorrhagic transformation of brain infarction (15 days): confirmed by cerebral CT scan	CG92
Sherman 2007[176]	Intervention (n=884): LMWH, enoxaparin 40mg once daily subcutaneously given for 10 days Comparison (n=878): UFH, 5000IU twice daily for 10 days Concomitant treatment: Usual care normally included antiplatelet, taken by 92% LMWH arm and 90% UFH arm.	n=1762 People within 48 hours of an acute ischaemic stroke, unable to mobilise independently Age (mean): 66 years Gender (male to female ratio): 1.29:1 200 centres in 15 countries	All-cause mortality (90 days) DVT (symptomatic and asymptomatic) (14 days): asymptomatic patients confirmed by bilateral contrast venography within 72 hours of last dose of study medication. Ultrasonography used for people who were unable to do venography. PE (14 days): no definition reported Major bleeding (14 days): 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	Included in CG92 Intracranial bleeding used as indirect outcome for haemorrhagic transformation of ischaemic stroke.

Study	Intervention and comparison	Population	Outcomes	Comments
		225	decompression of closed space to stop or control event, bleeding in retroperitoneal or intraocular location	
			Fatal PE (14 days): confirmed by autopsy	
			Minor clinically relevant bleeding (14 days): 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 haematoma or haemorrhagic wound complications not associated with features of over haemorrhage classified as major or subconjuctival haemorrhage needing end of study treatment)	
			Neurological (intracranial) bleeding (14 days): within 48 hours of stopping treatment, symptomatic, confirmed by head CT or MRI scan, or autopsy	

Table 75: Clinical evidence summary: AES (above knee) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with AES (above-knee) (95% CI)
All-cause mortality	2615 (2 studies) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 1.11 (0.88 to 1.42)	88 per 1000	10 more per 1000 (from 11 fewer to 37 more)
DVT (symptomatic and asymptomatic)	2615 (2 studies) 30 days	MODERATE[a] due to risk of bias	RR 0.9 (0.76 to 1.07)	179 per 1000	18 fewer per 1000 (from 43 fewer to 12 more)
PE	2615 (2 studies) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.65 (0.33 to 1.31)	15 per 1000	5 fewer per 1000 (from 10 fewer to 5 more)
Fatal PE	2518 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.00 (0.06 to 16.07)	1 per 1000	0 fewer per 1000 (from 1 fewer to 12 more)
Mechanical complications - skin breaks	2518 (1 study) 30 days	MODERATE[a] due to risk of bias	RR 4.02 (2.34 to 6.91)	13 per 1000	38 more per 1000 (from 17 more to 75 more)
Mechanical complications - foot ischaemia	2518 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 3.52 (0.73 to 16.9)	2 per 1000	4 more per 1000 (from 0 fewer to 25 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 76: Clinical evidence summary: AES (thigh-length) versus AES (knee-length)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Risk with AES (knee-length)	Risk difference with AES (thigh-length) (95% CI)
				Anticipated absolute effects	
All-cause mortality	3114 (1 study) 30 days	MODERATE[a] due to imprecision	RR 1.05 (0.87 to 1.28)	111 per 1000	6 more per 1000 (from 14 fewer to 31 more)
DVT (symptomatic and asymptomatic)	3114 (1 study) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.84 (0.7 to 1.02)	135 per 1000	22 fewer per 1000 (from 41 fewer to 3 more)
PE	3114 (1 study) 30 days	MODERATE[b] due to risk of bias	RR 0.31 (0.19 to 0.49)	48 per 1000	33 fewer per 1000 (from 24 fewer to 39 fewer)
Mechanical complications - discontinued due to skin concerns	3114 (1 study) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.82 (0.59 to 1.14)	48 per 1000	9 fewer per 1000 (from 20 fewer to 7 more)
Mechanical complications - discontinued due to discomfort	3114 (1 study) 30 days	MODERATE[b] due to risk of bias	RR 1.66 (1.26 to 2.18)	49 per 1000	33 more per 1000 (from 13 more to 58 more)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 77: Clinical evidence summary: IPCD (full leg) versus no prophylaxis

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with No prophylaxis	Risk difference with IPCD (full-leg) (95% CI)
All-cause mortality	2876 (1 study) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.83 (0.68 to 1.01)	131 per 1000	22 fewer per 1000 (from 42 fewer to 1 more)
DVT (symptomatic and asymptomatic)	2902 (2 studies) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.77 (0.66 to 0.90)	214 per 1000	49 fewer per 1000 (from 21 fewer to 73 fewer)
PE	2876 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.83 (0.51 to 1.35)	24 per 1000	4 fewer per 1000 (from 12 fewer to 9 more)
Mechanical complications - skin breaks	2876 (1 study) 30 days	LOW[a] due to risk of bias	RR 2.2 (1.3 to 3.71)	14 per 1000	17 more per 1000 (from 4 more to 38 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 78: Clinical evidence summary: IPCD + AES versus UFH + AES

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH + AES	Risk difference with IPCD + AES (95% CI)
All-cause mortality	237 (1 study) 22 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (20 fewer to 20 more)[c]
DVT (symptomatic and asymptomatic)	237 (1 study) 22 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.64 (0.55 to 4.87)	42 per 1000	27 more per 1000 (from 19 fewer to 161 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH + AES	Risk difference with IPCD + AES (95% CI)
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
c Zero events in both arms. Risk difference calculated in Review Manager.					

Table 79:   Clinical evidence summary: IPCD + AES versus AES alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with IPCD + AES (95% CI)
All-cause mortality	383 (2 studies) 90 days	LOW[a,b] due to risk of bias, imprecision	RR 0.65 (0.37 to 1.14)	125 per 1000	44 fewer per 1000 (79 fewer to 17 more)
DVT (symptomatic and asymptomatic)	365 (2 studies) 22 days	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.65 (0.15 to 2.79)	92 per 1000	32 fewer per 1000 (from 79 fewer to 165 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c Downgraded by 1 increment I^2 over 50% and subgroups do not explain heterogeneity. Analysed using random effects model.

Table 80:   Clinical evidence summary: UFH + AES versus AES alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with UFH + AES (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with UFH + AES (95% CI)
All-cause mortality	235 (1 study) 22 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (20 fewer to 20 more)
DVT (symptomatic and asymptomatic)	235 (1 study) 22 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.8 (0.25 to 2.54)	52 per 1000	10 fewer per 1000 (from 39 fewer to 80 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Zero events in both arms. Risk difference calculated in Review Manager.

Table 81: Clinical evidence summary: UFH versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with UFH (95% CI)
All-cause mortality	337 (2 studies) 28 days	LOW[a,b] due to risk of bias, imprecision	RR 0.65 (0.45 to 0.94)	328 per 1000	115 fewer per 1000 (from 20 fewer to 180 fewer)
DVT (symptomatic and asymptomatic)	402 (3 studies) 28 days	MODERATE[a] due to risk of bias	RR 0.29 (0.21 to 0.40)	638 per 1000	453 fewer per 1000 (from 383 fewer to 504 fewer)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 82: Clinical evidence summary: LWMH (standard dose; standard duration) versus no prophylaxis

Outcomes	No of	Quality of the	Relative effect	Anticipated absolute effects	

	Participants (studies) Follow up	evidence (GRADE)	(95% CI)	Risk with No prophylaxis	Risk difference with LMWH (95% CI)
All-cause mortality	163 (2 studies) 14 days	LOW[a,b] due to risk of bias, imprecision	RR 2.63 (1.02 to 6.81)	62 per 1000	101 more per 1000 (from 1 more to 359 more)
DVT (symptomatic and asymptomatic)	149 (2 studies) 14 days	LOW[a,b,c] due to risk of bias, imprecision, inconsistency	RR 0.72 (0.31 to 1.66)	400 per 1000	112 fewer per 1000 (from 276 fewer to 264 more)
PE	60 (1 study) 14 days	VERY LOW[a,b,d] due to risk of bias, indirectness and imprecision	RR 0.50 (0.05 to 5.22)	67 per 1000	33 fewer per 1000 (from 63 fewer to 281 more)
Major bleeding	103 (1 study) 14 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[e]	Not estimable[e]	0 fewer per 1000 (from 40 fewer to 40 more)[e]
Fatal PE	103 (1 study) 14 days	VERY LOW[a,b,d] due to risk of bias, indirectness and imprecision	Peto OR 0.13 (0.00 to 6.69)	20 per 1000	17 fewer per 1000 (from 20 fewer to 98 more)
Haemorrhagic transformation	103 (1 study) 15 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.39 (0.33 to 5.89)	58 per 1000	22 more per 1000 (from 39 fewer to 282 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c Downgraded by 1 increment due to inconsistency. I^2 over 50% and subgroups do not explain heterogeneity.

d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

e Zero events in both arms. Risk difference calculated in Review Manager.

Table 83: Clinical evidence summary: LMWH (standard dose; standard duration) versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with LMWH (95% CI)
All-cause mortality	998 (1 study) 90 days	LOW[a] due to imprecision	RR 1.00 (0.71 to 1.41)	118 per 1000	0 fewer per 1000 (from 34 fewer to 48 more)
DVT (symptomatic and asymptomatic)	998 (1 study) 15 days	MODERATE[a] due to imprecision	RR 0.32 (0.09 to 1.19)	18 per 1000	12 fewer per 1000 (from 17 fewer to 3 more)
PE	998 (1 study) 15 days	LOW[a] due to imprecision	RR 0.97 (0.24 to 3.85)	8 per 1000	0 fewer per 1000 (from 6 fewer to 23 more)
Major bleeding	998 (1 study) 15 days	LOW[a] due to imprecision	RR 0.97 (0.14 to 6.85)	4 per 1000	0 fewer per 1000 (from 4 fewer to 24 more)
Modified Rankin Scale Score 0-2	998 (1 study) 90 days	LOW[a] due to imprecision	RR 0.88 (0.76 to 1.03)	420 per 1000	50 fewer per 1000 (from 101 fewer to 13 more)
Barthel Index Score 60-100	998 (1 study) 90 days	LOW[a] due to imprecision	RR 0.95 (0.86 to 1.04)	652 per 1000	33 fewer per 1000 (from 91 fewer to 26 more)
Heparin-induced thrombocytopenia	998 (1 study) 15 days	LOW[a] due to imprecision	RR 0.97 (0.14 to 6.85)	4 per 1000	0 fewer per 1000 (from 4 fewer to 24 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 84: Clinical evidence summary: LMWH (standard dose; standard duration) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH	Risk difference with LMWH (95% CI)
All-cause mortality	2519 (3 studies) 90 days	MODERATE[a] due to risk of bias	RR 0.96 (0.77 to 1.19)	116 per 1000	5 fewer per 1000 (from 27 fewer to 22 more)
DVT (symptomatic and asymptomatic)	1483 (2 studies) 14 days	MODERATE[a] due to risk of bias	RR 0.57 (0.44 to 0.73)	192 per 1000	82 fewer per 1000 (from 52 fewer to 107 fewer)
PE	2092 (3 studies) 14 days	LOW[a,b] due to risk of bias, imprecision	RR 0.33 (0.1 to 1.11)	10 per 1000	7 fewer per 1000 (from 9 fewer to 1 more)
Major bleeding	2506 (3 studies) 14 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.34 (0.61 to 2.94)	9 per 1000	3 more per 1000 (from 3 fewer to 17 more)
Fatal PE	2092 (3 studies) 14 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.42 (0.1 to 1.87)	5 per 1000	3 fewer per 1000 (from 4 fewer to 4 more)
Clinically relevant non-major bleeding	1961 (2 studies) 14 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.87 (0.59 to 1.27)	55 per 1000	7 fewer per 1000 (from 23 fewer to 15 more)
Heparin-induced thrombocytopenia	545 (1 study) time-point not reported	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.51 (0.05 to 4.69)	7 per 1000	4 fewer per 1000 (from 7 fewer to 26 more)
Neurological bleeds - haemorrhagic transformation only	212 (1 study) 14 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 7.39 (0.15 to 372.38)	-	-[d]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH	Risk difference with LMWH (95% CI)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
c Downgraded by 1 increment because the majority of the evidence had indirect outcomes (includes primary bleeds)					
d Absolute effects could not be calculated due to zero events in one of the arms.					

15.4 Economic evidence

Published literature

One health economic study was identified with the relevant comparison. This study was published in three papers,[32, 47, 48] the earliest paper was included in CG92 addendum published in June 2015.[32] The study is summarised in the health economic evidence profile below (Table 85) and the health economic evidence table in appendix J.

See also the health economic study selection flow chart in appendix F.

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Table 85: Health economic evidence profile: IPCD (thigh length) + usual care vs usual care only

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
CLOTS trials Collaboration 2014[32], Dennis 2015[48] and Dennis 2015[47]([UK])	Directly applicable	Potentially serious limitations [(a)]	**-Study design**: Cost-utility analysis alongside a randomised controlled trial. **-Population**: immobile stroke patients **-Interventions**: **Intervention 1:** Usual care only. Routine care defined as early mobilisation hydration and antiplatelet or anticoagulant medication. **Intervention 2:** Thigh-length IPCD in addition to usual care. IPCD with thigh-length sleeves worn continuously on both legs for 30 days or next CDU (if >30 days) or until the patient was independently mobile, discharged from randomising hospital or refused to wear the sleeves or the staff became concerned about his/her skin condition.	2 vs 1 £451	2 vs1 +0.9 quality-adjusted life-days	ICER: £611 per quality-adjusted life-day (£223,168 per QALY)[(b)]	Sensitivity analyses did not alter the conclusion. Subgroup analysis based on predicted prognosis at randomisation showed that IPCD appeared to reduce the risk of DVT and probably improve survival in all immobile stroke patients except those in the fifth quintile (those with best prognosis). The authors concluded that IPCD is likely to be most effective in the subgroups of immobile stroke patients In the three intermediate quintiles.

Abbreviations: DVT: deep vein thrombosis; ICER: incremental cost-effectiveness ratio; IPCD: intermittent pneumatic compression device; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Most of the cost difference was derived from a per diem amount applied to a non- significant difference in length of stay rather than the actual cost of the hospital stay. Important costs were excluded from the analysis such as readmissions, post-hospital care, deep vein thrombosis, and pulmonary embolism. The timeframe was only 6 months which is unlikely to be sufficient to capture important cost and health consequences. The statistical methods used to estimate quality of life at baseline was experimental and had not been independently verified. The EQ-5D-3L generic quality of life measurement tool was known to have limitations in detecting small functional improvements in severely disabled people. There is a high degree of uncertainty around the estimates provided.

(b) Calculated by NGC.

15.5   Evidence statements

Clinical

AES (above-knee) versus no prophylaxis

Two studies comprising 2615 participants reported data for all-cause mortality, DVT (symptomatic and asymptomatic) and PE. There was no clinical difference between AES (above-knee) and no prophylaxis for DVT (symptomatic and asymptomatic). There was possible clinical harm of AES (above-knee) in terms of all-cause mortality, although the uncertainty around this result was also consistent with no difference. There was possible clinical benefit of AES (above-knee) in terms of PE, however the uncertainty around this result was also consistent with no difference or clinical harm. The quality of evidence ranging from very low to moderate due to risk of bias and imprecision. One study comprising 2518 people reported data for fatal PE and mechanical complications (skin breaks and foot ischaemia). Moderate quality precise evidence showed clinical harm of AES in terms of skin breaks. For fatal PE and foot ischaemia these outcomes also suggested a clinical harm with AES, although they were very uncertain and consistent with both no difference and clinical benefit as well. The quality of evidence was very low to moderate due to risk of bias and imprecision.

AES (thigh-length) versus AES (knee-length)

One study comprising 3114 participants reported all-cause mortality, DVT (symptomatic and asymptomatic), PE and mechanical complications (skin concerns and discomfort). There was clinical benefit of AES (thigh-length) in terms of the outcome of PE. Contrastingly there was clinical harm of AES (thigh-length) in terms of the mechanical complication of discomfort and suggested clinical harm in terms of all-cause mortality, although there was uncertainty around the mortality outcomes meaning it could also be consistent with no difference. There was no clinical difference between the two interventions in terms of DVT and mechanical complication of skin concerns, however the uncertainty around these results were also consistent with clinical harm. The quality of the evidence ranged from low to moderate due to risk of bias and imprecision.

IPCD (full leg) versus no prophylaxis

One study comprising 2876 participants reported low quality evidence for all-cause mortality, presenting possible clinical benefit of IPCD over no prophylaxis, however the uncertainty around this result was also consistent with no difference. Two studies comprising 2902 participants reported low quality evidence for DVT (symptomatic and asymptomatic); presented no clinical difference, although the confidence intervals around this result were also consistent with clinical benefit. One study comprising 2876 participants reported data for PE, presented no clinical difference but there was large uncertainty around the result, quality of evidence was very low due to risk of bias and imprecision. One study compromising 2876 participants reported data for a mechanical complications (skin break) showed clinical harm of IPCD (full-leg), quality of evidence was low due to risk of bias.

IPCD + AES versus UFH + AES/ IPCD + AES versus AES/UFH + AES versus AES alone

One three-arm study comprising 352 participants reported data for all-cause mortality and DVT (symptomatic and asymptomatic) comparing IPCD in combination with AES, UFH in combination with AES and AES alone.

For the comparison, of IPCD in combination with AES versus UFH in combination with AES, there was no clinical difference in terms of all-cause mortality and possible clinical harm of IPCD in combination with AES in terms of DVT (symptomatic and asymptomatic), although there was very serious imprecision around this result suggesting both no difference and possible clinical benefit as well. The quality of evidence was very low due to risk of bias and imprecision.

For the comparison of IPCD in combination with AES versus AES alone there was an additional study, which reported the same outcomes of all-cause mortality and DVT (symptomatic and asymptomatic). The combined evidence from two studies, suggested possible clinical benefit of IPCD in combination with AES in terms of all-cause mortality and DVT (symptomatic), although the imprecision also suggested that there could have been no difference for mortality, and both no difference and possible harm for DVT. The quality of evidence was very low due to risk of bias and imprecision.

There was also no clinical difference in terms of DVT (symptomatic and asymptomatic) and all-cause mortality, for the comparison evaluating UFH in combination with AES versus AES alone, although the uncertainty around these results was very high and also consistent with harm or benefit. The quality of evidence was very low due to risk of bias and imprecision.

UFH versus no prophylaxis

Across three studies comprising 402 participants data was reported for all-cause mortality and DVT (symptomatic and asymptomatic). Low quality evidence suggested clinical benefit of UFH for all-cause mortality, although with the uncertainty this result could also be consistent with no difference. Moderate quality evidence showed clinical benefit in terms of DVT (symptomatic and asymptomatic).

LMWH (standard dose) versus no prophylaxis

Data was reported for all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE and haemorrhagic transformation across two studies comprising 163 participants. There was possible clinical harm of LMWH in terms of all-cause mortality and haemorrhagic transformation, although these findings were uncertain and therefore also consistent with no difference, or in the case of haemorrhagic transformation, also clinical benefit. There was possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic) and fatal PE, although these findings were seriously imprecision, and could also be consistent with no difference or harm. There was no clinical difference in terms of major bleeding. Quality of the evidence ranged from very low to low due to risk of bias, imprecision, indirectness and inconsistency.

LMWH (standard dose) versus aspirin

One study comprising 999 participants reported data for all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, health-related quality of life (modified Rankin Scale and Barthel Index) and heparin-induced thrombocytopenia. There was no clinical difference between LMWH at a standard dose for a standard duration and aspirin in terms of all-cause mortality, PE, major bleeding, both of the health-related quality of life measures and heparin-induced thrombocytopenia. However the uncertainty around the effect estimates for all these outcomes showed consistency with both harm and benefit as well as no difference. There was possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic), although this finding was also consistent with no difference when taking uncertainty into account. Quality of the evidence ranged from low to moderate due to imprecision.

LMWH (standard dose) versus UFH

Three studies comprising an overall 2519 participants reported data for all-cause mortality, PE, major bleeding and fatal PE. Two studies comprising overall 1961 participants reported data for DVT (symptomatic and asymptomatic) and clinically relevant non-major bleeding. One study comprising 545 participants reported data for heparin-induced thrombocytopenia, another study comprising 212 participants reported data for haemorrhagic transformation. Moderate quality, precise evidence showed clinical benefit of LMWH at a standard dose for a standard duration in terms of DVT (symptomatic and asymptomatic). There was possible clinical benefit in terms of all-cause mortality, PE, fatal PE and heparin-induced thrombocytopenia, although these findings were also consistent with no difference when taking uncertainty into account. Contrastingly, there was possible clinical harm of LMWH at a standard dose and for a standard duration in terms of major bleeding and haemorrhagic transformation. However there was very serious imprecision around these results, expanding the possibility to also include no difference and clinical benefit. There was no clinical difference between the two interventions in terms of clinically relevant non-major bleeding. The quality of evidence in this comparison ranged from very low to moderate due to risk of bias, imprecision and indirectness.

Economic

• One cost–utility analysis found that in immobile stroke patients thigh- length Intermittent pneumatic compression device (IPCD) in addition to usual care was more effective and more costly (ICER: £223,168 per QALY) compared to usual care alone for preventing VTE in immobile stroke patients. This analysis was assessed as directly applicable with potentially serious limitations.

15.6   Recommendations and link to evidence

Recommendations	**1.4.2 Do not offer anti-embolism stockings for VTE prophylaxis to people who are admitted for acute stroke. [2010, amended 2018]** **1.4.3 Consider intermittent pneumatic compression for VTE prophylaxis for people who are immobile and admitted with acute stroke. If using, start it within 3 days of acute stroke. [2018]** **1.4.4 Explain to the person admitted with acute stroke and their family members or carers (as appropriate) that intermittent pneumatic compression:** • **reduces the risk of deep vein thrombosis and may increase their chances of survival** • **will not help them recover from stroke, and there may be an associated increased risk of surviving with severe disability. [2018]** **1.4.5 When using intermittent pneumatic compression for people who are admitted with acute stroke, provide it for 30 days or until the person is mobile or discharged, whichever is sooner. [2018]**
Research recommendation	**None**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (7–90 days from hospital discharge), pulmonary embolism (7–90 days from hospital discharge), major bleeding (up to 45 days from hospital discharge) and fatal PE (7-90 days from

	hospital discharge) as critical outcomes.
	The committee considered health-related quality of life (up to 90 days from hospital discharge), clinically relevant non-major bleeding (up to 45 days from hospital discharge), heparin-induced thrombocytopenia (duration of study), technical complications of mechanical interventions (duration of study) and haemorrhagic transformation (for people without haemorrhagic stroke only) (up to 45 days from hospital discharge) as important outcomes.
	Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	Seventeen randomised controlled trials were included in this review. Fifteen of these studies were included in the previous guideline (CG92), five of which were extracted from two systematic reviews. Two new studies were added to the review.
	Thirteen comparisons were included in this review, evaluating the use of pharmacological (UFH, LMWH and aspirin) and mechanical (AES and IPCD) interventions for VTE prophylaxis.
	Across the evidence, quality was downgraded due to risk of bias based primarily on the amount of missing data present within the included studies. In some cases there were also measurement issues in terms of the reliable ascertainment of VTE event rates.
	The committee agreed that it would be reasonable to use the outcome of intracranial bleeding as an indirect outcome for haemorrhagic transformation of ischaemic stroke.
Trade-off between clinical benefits and harms	The committee noted that there was no evidence identified for the use of foot impulse devices (FID) or neuromuscular electrical stimulation (NMES). No evidence that met the inclusion criteria was available relating to the benefits or harms of the devices and so it was agreed not to make a recommendation regarding these devices. The importance of the clinician's judgement and weighing of the risks and benefits of VTE prophylaxis in the stroke population was discussed in length.
	Patients are likely to be relatively immobile after stroke and therefore are predisposed to an increased risk of VTE. The committee agreed that this risk should be balanced against the risk of bleeding, including haemorrhagic transformation which can have very serious consequences. In addition, the risk of bleeding on admission may not be known. Therefore caution should be applied before considering pharmacological prophylaxis. Patients with haemorrhagic stroke have already experienced bleeding into a critical location (brain) while patients with ischaemic stroke are also at risk of haemorrhagic transformation. The committee agreed that bleeding was a more immediate risk for this population than the risk of developing VTE and measures should be taken to prevent increasing this risk. Pharmacological prophylaxis is likely to increase additional bleeding risk and may lead to long-term morbidity in this population. The committee did not consider that the current evidence demonstrated a strong enough positive effect on VTE outcomes to warrant recommending pharmacological prophylaxis in this population where bleeding would have catastrophic consequences.
	The committee recognised that the evidence reported from the studies evaluating mechanical interventions was inconclusive but noted that the more clinically beneficially mechanical intervention is IPCD. The committee acknowledged concerns from stakeholders expressed during previous guideline public consultation, that a large proportion of stroke patients, at high risk for VTE and contraindicated for pharmacological prophylaxis, may be left without protection. The committee therefore agreed that the recommendation relating to the use of IPCD (from CG92 and the CG92 stroke population addendum) is still applicable. The recommended duration for IPCD is longer than in other hospital populations due to the extended period for which people are likely to be immobile and bedridden following an acute

	stroke. The 30-day duration is taken from the intervention arm of the larger trial contributing to the evidence base in the review (CLOTS-3 trial). One topic expert noted that if a decision is made to use IPCD, it should not be withdrawn if the patient is transferred within 30 days to another hospital bed unless they are mobile. The recommended time-point for starting VTE prophylaxis with IPCD (within 3 days of aute stroke), was also taken from the intervention arm of the larger trial contributing to the evidence base in the review (CLOTS-3 trial).
	Intermittent pneumatic compression devices do not increase the risk of bleeding but may cause damage to the skin. The committee noted that skin breaks are a less important outcome than others under consideration, but may necessitate stopping IPCD and can be potentially difficult to treat in immobile older people.
	The committee highlighted that there is additional evidence from the CLOTS-3 study when considering outcomes measured at a longer term than those considered in the current update review protocols. This suggests use of IPC may be associated with an increased risk of surviving with severe disability, as measured by the Oxford Handicap Scale (a categorical scale measuring functional outcome after stroke). The evidence reports that 38 more people per 1000 may be severely disabled (totally dependent, requiring constant attention day and night) 6 months after acute stroke when they received standard best practice care plus IPC compared to those who received standard best practice care without IPC.
Trade-off between net clinical effects and costs	One economic study, published in three papers, was included in the evidence review. This was a cost-utility analysis alongside the CLOTS-3 trial. The results of the main trial analysis were presented in the first two papers, one of which has been previously included in the CG92 addendum. The results showed that use of IPCD in addition to usual care compared to usual care alone resulted in a net health gain of 0.9 quality adjusted life days (95% CI -2.1 to +3.9). This was combined with the mean incremental cost difference of £451 greater for the IPCD arm to result in an incremental cost-effectiveness ratio of £611 per quality adjusted life day. This equates to £223,168 per QALY-gained. The study was assessed as directly applicable with potentially serious limitations.
	The following limitations of the CLOTS-3 economic analysis, which were previously considered by the CG92 addendum committee, were discussed by the committee. These were that:
	•Most of the cost difference was derived from a per day amount applied to a non-significant difference in length of stay rather than the actual cost of the hospital stay.
	•Important costs were excluded from the analysis such as readmissions, post-hospital care, deep vein thrombosis, and pulmonary embolism.
	•The time horizon was only 6 months which is unlikely to be sufficient to capture important cost and health consequences.
	•The statistical methods used to estimate quality of life at baseline were experimental and had not been independently verified.
	•The EQ-5D-3L generic quality of life measurement tool was known to have limitations in detecting small functional improvements in severely disabled people.
	•There is a high degree of uncertainty around the estimates provided.
	The committee determined that these limitations weaken the analysis and cast doubt on the reported ICER. The committee also noted that the most recently published paper from the CLOTS-3 trial economic analysis attempted to conduct a subgroup analysis to identify a cohort of patients that IPCD would become cost-effective for. However, the prognostic model proposed in this paper cannot be easily implemented on a large scale in the NHS to identify patients for which IPCD is considered to be cost-effective. Hence, the committee agreed that there was no need to change the CG92 addendum recommendation for using IPCD in stroke patients. The duration of using IPCD was recommended based on the duration in the

	CLOTs-3 study, however, the committee acknowledged that for some people with stroke the duration of immobilisation will be longer and the decision to continue using IPCD beyond this duration will need to be made on individual basis.
Other considerations	Overall, the committee regarded the risk/benefit trade-off such that there is likely to be sufficient overall health gain to justify considering use of IPCD in this population. Stakeholder comments following CG92 and the June 2015 addendum expressed concerns that a large proportion of stroke patients, at high risk of VTE and contraindicated for pharmacological prophylaxis, may be left without protection, emphasising the need for VTE prophylaxis in the stroke population. NHS Improving Quality Programme (NHS IQ)[135] has recognised the importance of reducing mortality from VTE in the stroke population. NHSA IQ has secured £1m 'pump priming' money from 1 April 2014 to fund a six months' supply of intermittent pneumatic compression (IPC) sleeves for all stroke units in England.
	During the development of the June 2015 addendum, it was agreed that clinicians should carefully consider the potential benefits versus risks for each individual patient as part of an informed discussion with the patient where possible, or with their relative or carer.
	The committee noted that people who have a stroke within hospital will be administered an antiplatelet agent as part of their treatment. The committee did not think it was necessary to recommend further pharmacological prophylaxis to stroke patients in addition to antiplatelet agents.

16 Acutely ill medical patients admitted to hospital

16.1 Introduction

Many medical patients have more than one risk factor for VTE. Apart from being an older cohort, other risk factors reported include previous VTE, cancer, stroke, heart failure, chronic obstructive airways disease, sepsis and bed rest. At the time the previous guideline (CG92) was written the uptake of thromboprophylaxis in medical patients was poor. Following the publication of CG92 with the details of the National VTE Risk Assessment Tool, it is now estimated that 73% of medical patients receive VTE prophylaxis (NHS Safety Thermometer Data – March 2016 to March 2017, published April 12, 2017; accessed 15 August 2017).

16.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for acutely ill medical patients admitted to hospital?

For full details see review protocol in appendix C.

Table 86: PICO characteristics of review question

Population	Adults and young people (16 years and older) who are acutely ill medical patients admitted to hospital

Intervention(s)	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:
	  o warfarin (variable dose only)
	  o acenocoumarol (all doses)
	  o phenindione (all doses)
	• Fondaparinux (all doses)*
	• Apixaban (all doses)*
	• Dabigatran (all doses)*
	• Rivaroxaban (all doses)*
	• Aspirin (up to 300mg)*
	
	*off-label

Comparison(s)	Compared to: • Other VTE prophylaxis treatment • No VTE prophylaxis treatment • Placebo Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Low versus high dose for LMWH only Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge
Outcomes	Critical outcomes: • All-cause mortality (up to 90 days after line removed) • Deep vein thrombosis (DVT) (symptomatic and asymptomatic) (7-90 days after line removed). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) • Pulmonary embolism (PE) (7 - 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 ≥2g/dl; a serious or life threatening clinical event • 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: • 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 (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.

16.3 Clinical evidence

Twenty studies describing seventeen trials were included in the review. Nine studies [35 43 71 94 98 100 101 108 169] were previously included in the previous guideline (CG92) and eleven studies [36 60 66 81 82 87 117 160 184 172 173] were added in the update. These are summarised in **Table 87** below. Evidence from these studies is summarised in the clinical evidence summary tables below. See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

One Cochrane review [6] was identified which looked at heparin for the prevention of venous thromboembolism in acutely ill medical patients, however the review protocol differed slightly and the Cochrane could therefore not be included in full.

Summary of included studies

Table 87:   Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Cohen 2006 [35]	Intervention (n= 429): Fondaparinux, 2.5 mg in 0.5 ml saline given subcutaneously once daily. Start time: within 48 hours of admission. End time: 1-13 days (median 7 days) Comparison (n= 420): Placebo, 0.5 ml isotonic saline subcutaneously given once daily Start time: within 48 hours of admission End time: 1-13 days (median 7 days) Concomitant treatment: AES and physiotherapy were allowed (no information about how many used this)	n=849 Older people hospitalised for acute medical conditions Congestive heart failure (25%) acute respiratory distress (19.7%), acute infectious or inflammatory disease (25.2%) (as reported in CG92) Age (mean): 74.7 years Gender (male to female ratio): 1:1.36 35 centres in 8 countries (no further information about countries)	All-cause mortality (30 days) Fatal PE (30 days): confirmed by autopsy or no other explainable reason DVT (symptomatic and asymptomatic) (15 days): confirmed by venography Symptomatic PE (30 days): confirmed by high probability lung scan, pulmonary angiography or helical computed tomography Major bleeding (15 days): bleeding in a critical location, bleeding leading to surgical intervention, overt bleeding associated with a drop in haemoglobin concentration of ≥20 g/l or leading to transfusion of 2 or more units of red blood cells	Included in CG92
Cohen 2013 [36]	Intervention (n=4050): Rivaroxaban, 10mg	n= 8101 People hospitalised	All-cause mortality (35 days)	New study

Study	Intervention and comparison	Population	Outcomes	Comments
	once daily subcutaneously for 35±4 days. Subcutaneous placebo given for 10±4 days Comparison (n=4051): LMWH, enoxaparin 40 mg (standard dose) once daily, subcutaneously for 10±4 days. Oral placebo was given for 35±4 days	for acute medical conditions. Infectious disease 45.5%; Heart failure 32.4%; Respiratory insufficiency 28%; Ischaemic stroke 17.3%; Active cancer 7.3%; Inflammatory or rheumatic disease 3.8%; ≥ 2 medical conditions 31% Age (median): 71 years Gender (male to female ratio): 1.18/1 Multicenter, 556 sites in 52 countries (no further details about countries involved in the study)	DVT (symptomatic and asymptomatic) (35 days): definition not reported PE (35 days): definition not reported Major bleeding (35 days): Bleeding leading to a ≥2 g/dl fall in hemoglobin 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	Combined asymptomatic proximal DVT and symptomatic proximal or distal DVT
Dahan 1986 [43]	Intervention (n=135): LMWH, enoxaparin, 60 mg (high dose) in a volume of 0.3 ml started on admission and continued for 10 days. Comparison (n=135): Placebo (no further details reported)	n=270 Older people hospitalised for acute medical conditions Medical conditions: heart failure 19%, respiratory diseases 22%, ischaemic stroke 18%, malignant diseases 13.5%, diabetes 4.6%, depression 3.9%, syncope 5%, infection 4.2%, neurologic diseases 2.7%, joint diseases 2.7%, hepatic or biliary diseases 1.5%, miscellaneous 3.1% Age: >65 years; mean: 80.1 years Gender (male to female ratio): 1.6:1	All-cause mortality (10 days) DVT (symptomatic and asymptomatic) (10 days): diagnosed by fibrinogen uptake test Fatal PE (10 days): diagnosed by autopsy	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
		France		
Goldhaber 2011 [60]	Intervention (n=3255): Apixaban, 2.5 mg twice daily administered orally. Received daily injections of a placebo for a minimum of 6 days. Duration: 30 days. Comparison (n=3273): LMWH, enoxaparin 40 mg (standard dose), administered subcutaneously once daily during their stay in the hospital, for a minimum of 6 days.	n=6528 People hospitalised for acute medical conditions with congestive heart failure (39%), acute respiratory failure (37.1%), infection (without septic shock) (22.2%), acute rheumatic disorder (1.2%), or inflammatory bowel disease (0.8%) and had an expected hospital stay of at least 3 days. Age (mean): 67.5 years Gender (male to female ratio): 1:1.04 Multicentre , 302 centres in 35 countries (no further details about countries involved in the study)	All-cause mortality (30 days): PE (60 days): confirmed by with the use of systematic bilateral compression ultrasonography Major bleeding (30 days): fatal or overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of 2 g or more per deciliter over a 24-hour period; transfusion of 2 or more units of packed red cells; or intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding, bleeding that occurred in an operated joint that required reoperation or intervention, or intramuscular bleeding with the compartment syndrome. Clinical relevant non-major bleeding (30 days): 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 hematuria or hematuria persisting for 24 hours or more after urinary-tract catheterization, unusual	New study

Study	Intervention and comparison	Population	Outcomes	Comments
			bruising, radiographically confirmed hematoma, or hemoptysis.	
Harenberg 1996 [71]	Intervention (n=983): LMWH, nadroparin 36 mg (3100IU of antiXa), plus two placebo injections, 3 times daily, at 8 hour intervals Start time: within 12 hours of admission to hospital End time: 11 days Duration: 10 days Comparison (n=985): UFH, 5000IU subcutaneously given, 3 times daily at 8 hour intervals Start time: within 12 hours of admission to hospital End time: 11 days Duration: 10 days	n= 1968 People who have been hospitalised and are bed ridden, bed rest >10 days Main diagnosis: cardiac insufficiency 15%, cerebrovascular diseases 14.4%, coronary heart disease 13.7%, cancer 6.1%, diabetes 5.3%, gastrointestinal or nephrology disease 4.2%, chronic obstructive lung disease 4.42%, pneumonia or infections 2.13% Age (mean): 70.5 years Gender (male to female ratio): 1:1.8 Germany	All-cause mortality (time-point not reported) Fatal PE (time-point not reported): confirmed by perfusion scintigraphy, additional angiography or ventilation scintiscan performed if results were low probability defects PE (symptomatic) (time-point not reported): confirmed by perfusion scintigraphy, additional angiography or ventilation scintiscan performed if results were low probability defects Major bleeding (time-point not reported): no definition reported	Included in CG92
Hull 2010 [81]: EXCLAIM study	Intervention (n= 2975): LMWH, extended enoxaparin 40 mg/d (standard dose), subcutaneously given for 10 ± 4 days, then further course of enoxaparin for 28 ± 4 days. Comparison (n=2988): Placebo. Received enoxaparin subcutaneously 40 mg/d (standard dose) for 10 ± 4 days also.	n=5963 People hospitalised for acute medical conditions with recent reduced mobility, requiring total bed rest or being sedentary without bathroom privileges or with bathroom privileges. Acute infection without septic shock 33.2%; Acute respiratory insufficiency 30.3%;	All-cause mortality (90 days) PE (asymptomatic and symptomatic) (90 days): confirmed using computed tomography or ventilation–perfusion lung scanning Fatal PE (90 days): no definition reported	New study

Study	Intervention and comparison	Population	Outcomes	Comments
		Heart failure 18.7%; Post-acute ischaemic 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% Age (mean±SD): 67.9 ± 12.1 Gender (male to female ratio): 1:1 Multiple countries, 370 hospitals across 20 countries (no further details about countries involved in the study)		
Ishi 2013 [82]	Intervention (n=44): LMWH, enoxaparin 40mg (standard dose) subcutaneously given once daily. Continued until person became ambulant and ready for discharge. Comparison (n=48): UFH, 5000 IU subcutaneously given twice daily. Continued until person became ambulant and ready for discharge.	n=92 People hospitalised for acute medical conditions requiring at least 3 days of ICU stay or same duration non-ambulatory care in wards. Stroke 19.9%, cardiological dysfunction 4.8%, sepsis 11.7%, toxicological causes 26.3%, multisystem disorder 13%, others 15.2% Age (mean) : 54.4 years Gender (male to female ratio): 2.4:1 India	Major bleeding (time-point not reported): definition not reported) Heparin-induced thrombocytopenia (time-point not reported): not reported)	New study
Kakkar 2011 [87]	Intervention (n=4174): LMWH, enoxaparin 40	n=8319	All-cause mortality (90 days)	New study

Study	Intervention and comparison	Population	Outcomes	Comments
	mg (standard dose) once daily plus AES (knee-high) that provided graduated pressure from 15 mm Hg (at the ankle) to 10 mm Hg (at the knee).Duration: 10±4 days Comparison (n=4145): AES, knee-high, that provided graduated pressure from 15 mm Hg (at the ankle) to 10 mm Hg (at the knee) Placebo, received a subcutaneous injection with placebo (0.9% saline), once daily	People hospitalised for acute medical conditions 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%. Age (mean): 65.5 years Gender (male to female ratio): 1.7:1 Multicentre, 193 sites in China, India, Korea, Malaysia, Mexico, the Philippines, and Tunisia	Major bleeding (8 days): A 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 hemoglobin level of 20 g or more per liter; 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 (8 days): defined as a non-major hemorrhage leading to discontinuation of the study drug or to hospitalization.	
Kleber 2003 [94]	Intervention (n=332): LMWH, enoxaparin 40 mg (standard dose), subcutaneously given once daily Start time: on enrolment day Duration: 10±2 days Comparison (n=333): UFH, 5000IU 3 times daily, subcutaneously Start time: on enrolment day Duration: 10±2 days Concomitant treatment: People on	n=665 People hospitalised with heart failure (50%) and respiratory disease (50%), confined to bed >2/3 of the time Age (mean± SD): 70±14 years Gender (male to female ratio): 1.1:1 Germany	All-cause mortality (time-point not reported) Fatal PE (time-point not reported): confirmed by autopsy PE (symptomatic) (time-point not reported): confirmed by perfusion scintigram) DVT (symptomatic and asymptomatic) (time-point not reported): confirmed by: patients with positive D dimer or fibrin monomer test underwent bilateral venography or	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	anticoagulants or platelet inhibitors, or NSAIDS. Heart failure patients allowed 100 mg aspirin. AES applied up to 20% of patients in each treatment group		autopsy Major bleeding (time-point not reported): retroperitoneal or intracranial bleeding, overt bleeding with haemoglobin	
Lechler 1996 [98]	Intervention (n=477): LMWH, enoxaparin 40mg (standard dose), daily and 2 placebo injections (isotonic mannitol solution) (total of 3 injections daily) All injections were 0.2 ml Start time: within 24 hours of admission Duration: 7 days Comparison (n=482): UFH, 5000IU 3 times daily subcutaneously given.	n= 959 People hospitalised for acute medical conditions who are immobile Conditions including: cardiovascular diseases, endocrinologic diseases, respiratory diseases, gastrointestinal and urogenital diseases, central nervous diseases, cancer, bone diseases, skin diseases (percentages not reported) Age (mean± SD): 74±13 years Gender (male to female ratio): 1:1.64 Austria and Germany	All-cause mortality (not reported) PE (symptomatic) (time-point not reported): confirmed by: perfusion scan, angiography and autopsy in cases of death if permitted) DVT (symptomatic and asymptomatic) (time-point not reported): confirmed by duplex sonography at end of study period, or when clinically suspected. Positive cases were confirmed with phlebography Major bleeding (time-point not reported): confirmed by decrease in Hb≥2g/dl, transfusion of >2 units of blood and/or retroperitoneal or intracranial bleeding	Included in CG92
Lederle 2006 [100]	Intervention (n= 140): LMWH, enoxaparin 40 mg (standard dose), subcutaneously given daily. First injection given immediately after randomisation. Duration of treatment not reported Comparison (n=140): Placebo, identical syringes containing placebo. Duration of	n= 280 Older people (aged 60 years and over) hospitalised and admitted to medical wards, intensive care units or intermediate care Cancer 5%, cerebrovascular disease 8.6%, chronic obstructive lung disease 47.1%,	All-cause mortality (90 days) PE (symptomatic) (90 days): confirmed by ventilation perfusion scan, pulmonary angiogram or autopsy Major bleeding (time-point not reported): no definition reported Heparin-induced	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	treatment not reported	diabetes 27.9%, congestive heart failure 22.1%, myocardial infarction 25.7%, peripheral vascular disease 22% Age (mean): 71.7 years Gender (male to female ratio): 1:0 USA	thrombocytopenia (time-point not reported)	
Leizorovicz 2004 [101]	Intervention (n=1848): LMWH, dalteparin 5000 IU (standard dose), once daily for 14 days Comparison (n=1833): Placebo, once daily for 14 days Concomitant treatment: Low dose aspirin (up to 325 mg/day), ticlopidine and clopidogrel permitted	n=3681 People hospitalised for acute medical conditions, immobilised <3 days Acute congestive heart failure (NYHA class III or IV) 51%, acute respiratory failure 30%, infectious disease 37%, rheumatological disease 11%, inflammatory bowel disease 0.49% Age (mean): 68.5 years Gender (male to female ratio): 1:1.1 Multi-national (no further details about countries involved in the study)	All-cause mortality (90 days) PE (symptomatic) (90 days): no definition reported Major bleeding (21 days): no definition reported Fatal PE (21 days): confirmed by autopsy	Included in CG92
Mahe 2005 [108]	Intervention (n=1230): LMWH, nadroparin, 0.3ml (7500 AXa IU) subcutaneously started within 24 hours of hospitalisation and continued for 21 days or until discharge.	n=2474 People hospitalised for acute medical conditions who are bedridden acute cardiovascular	All-cause mortality (time-point not reported) Fatal PE (time-point not reported): confirmed by autopsy	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=1244): Placebo (not further details reported)	disease 13%, atrial fibrillation 12%, acute pulmonary disease 22%, cancer 14%, sepsis (not pulmonary) 23% Age (mean): 70.6 years Gender (male to female ratio): 1:1.47 France		
Miranda 2017 [117]	Intervention (n=46) LMWH, enoxaparin, 60mg once daily (high dose), subcutaneously given at 12pm for 14 days. Comparison (n=45): LMWH, enoxaparin, 60mg once daily (high dose), subcutaneously given at 12pm for 14 days.	n=91 Obese people hospitalised for acute medical conditions Mean BMI: 36.5 kg/m^2 acute infection 50%, acute rheumatic disorders 18%, acute respiratory failure 10.5%, acute congestive heart failure 9%, combined indications 14% Age (mean): 71 years Gender (male to female ratio): 1:1.2 France	All-cause mortality (14 days) Major bleeding (14 days): defined as fatal, intracranial or retroperitoneal haemorrhage, necessity of blood transfusion (2 units) or decrease of haemoglobin level greater than 2g/dL. Thrombocytopenia (14 days)	New study
Riess 2010 [160] CERTIFY trial (Haas 2011 [66] – cancer subgroup; Schellong 2011 [172] – older adults subgroup; Tebbe 2010 [184] – heart failure subgroup)	Intervention (n=1626): LMWH, certoparin 3,000 U anti Xa OD(standard dose), subcutaneously given, once daily. People within the certoparin treatment group also received two placebo injections. The intervention was given at regular intervals of 8 hours for 8-20 days.	n=3244 Older people hospitalised with acute medical condition and who have a significant decrease in mobility (bedridden or only able to walk short distances) expected for at least 4 days. Reasons for	All-cause mortality (90 days): definition not reported PE (90 days): confirmed by compression ultrasound sonography Major bleeding (time-point not reported): fatal bleeding, clinically overt bleeding associated with a fall of the haemoglobin concentration greater	New study

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=1618): 5000 IU UFH t.i.d., subcutaneously given, three times daily. The intervention was given at regular intervals of 8 hours for 8-20 days.	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% Age: >70 years; mean ±SD 79.0±6.1 years Gender (male to female ratio): 1.56:1 Germany	than 2 g/l compared to the baseline haemoglobin concentration, clinically overt bleeding that required transfusion of two or more units of packed red cells or whole blood, symptomatic bleeding in a critical area or organ (intracranial, intraspinal, retroperitoneal and pericardial). Heparin-induced thrombocytopenia (time-point not reported)	
Samama 1999 [169]	Intervention 1 (n=364): LMWH, enoxaparin 20 mg (low dose), subcutaneously given once daily. 20 mg of enoxaparin in 0.2 ml of water for injectable preparations. Start time: within 24 hours after randomisation Treatment scheduled to last 6-14 days Intervention 2 (n=367): LMWH, enoxaparin 40 mg (standard dose), subcutaneously given once daily. 40 mg of enoxaparin in 0.2 ml of water for injectable preparations. Start time: within 24 hours after randomisation Treatment scheduled to last 6-14 days Comparison (n=371): Placebo (0.2 ml of	n=1102 People hospitalised with acute medical condition Reasons for hospitalisation: NYHA class III chronic heart failure (CHF), NYHA class IV CHF, acute respiratory failure, acute infectious disease , acute rheumatic disorder, inflammatory bowel disease (number of people with each condition not clearly reported) Age (mean): 73.5 years Gender (male to female ratio): 1:1 International: 60 centres in 9 countries (no further details about countries involved in the study)	All-cause mortality (1-110 days) Fatal PE (1-110 days): confirmed by autopsy PE (symptomatic) (1-110 days): confirmed by high-probability lung scanning, pulmonary angiography, or helical computed tomography or at autopsy DVT (symptomatic and asymptomatic) (1-110 days): confirmed by systematic ascending contract venography of the legs between days 6 and 14, or earlier if thrombosis was clinically suspected. If venography was infeasible venous ultrasonography was performed. Major bleeding (days 1-14): definition not reported	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	isotonic water) Start time: within 24 hours after randomisation Treatment scheduled to last 6-14 days in the hospital Concomitant treatment: Elastic bandages or support stockings, and physiotherapy were used according to the usual practice at each centre (proportion of people within the study that used the stockings not reported)	255		
Schellong 2010 [173]	Intervention (n=163): LWMH, certoparin 3000 IU (standard dose), single daily dose during the treatment period Duration: 10±2 days Comparison (n=174): UFH, 7500 IU twice daily given subcutaneously during the treatment period Duration: 10±2 days	n=337 People hospitalised with acute medical condition and who have a significant recent decrease in mobility (completely bedridden or only able to walk short distances with the support of a nurse) Age: >40 years; mean±SD 70.6 ±12.3 years Gender (male to female ratio): Not reported Germany	All-cause mortality (90 days) DVT (symptomatic and asymptomatic) (90 days): assessed with the use of complete compression ultrasound (CCUS) of the lower extremity veins. PE (symptomatic and asymptomatic) (90 days: definition not reported Heparin-induced thrombocytopenia (90 days)	New study

Table 88: Clinical evidence summary: LMWH (standard dose; standard duration) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (95% CI)
All-cause mortality	6938 (4 studies) not reported- 110 days	LOW[a,b] due to risk of bias, indirectness	RR 0.97 (0.83 to 1.13)	85 per 1000	3 fewer per 1000 (from 14 fewer to 11 more)
DVT (symptomatic and asymptomatic)	535 (1 study) not reported - 110 days	LOW[a,b] due to risk of bias, indirectness	RR 0.39 (0.23 to 0.67)	160 per 1000	97 fewer per 1000 (from 53 fewer to 123 fewer)
PE (symptomatic or asymptomatic)	4013 (3 studies) not reported - 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.6 (0.25 to 1.45)	7 per 1000	3 fewer per 1000 (from 5 fewer to 3 more)
Major bleeding	4051 (3 studies) not reported	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.53 (0.8 to 2.92)	7 per 1000	4 more per 1000 (from 1 fewer to 13 more)
PE, fatal	4294 (3 studies) not reported - 90 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.58 (0.31 to 1.11)	9 per 1000	4 fewer per 1000 (from 6 fewer to 1 more)
Heparin-induced thrombocytopenia	280 (1 study) not reported	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.33 (0.04 to 3.17)	21 per 1000	14 fewer per 1000 (from 21 fewer to 46 more)
Clinically relevant non-major bleeding	8307 (1 study) 8 days	VERY LOW[a,c] due to risk of bias, imprecision	RR 1.27 (0.63 to 2.56)	3 per 1000	1 more per 1000 (from 1 fewer to 5 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (95% CI)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 89: Clinical evidence summary: LMWH (high dose; standard duration) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (high dose) (95% CI)
All-cause mortality	270 (1 study) 10 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.00 (0.33 to 3.02)	44 per 1000	0 fewer per 1000 (from 30 fewer to 90 more)
DVT (symptomatic and asymptomatic)	263 (1 study) 10 days	LOW[a,b] due to risk of bias, imprecision	RR 0.33 (0.11 to 1.00)	92 per 1000	61 fewer per 1000 (from 82 fewer to 0 more)
PE, fatal	263 (1 study) 10 days	VERY LOW[b] due to risk of bias, imprecision	RR 0.33 (0.03 to 3.14)	23 per 1000	15 fewer per 1000 (from 22 fewer to 49 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 90: Clinical evidence summary: LMWH (low dose; standard duration) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (low) (95% CI)
All-cause mortality	713	VERY LOW[a,b,c]	RR 1.05	138 per 1000	7 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (low) (95% CI)
	(1 study) 110 days	due to risk of bias, indirectness, imprecision	(0.73 to 1.51)		(from 37 fewer to 70 more)
DVT (symptomatic and asymptomatic)	526 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.05 (0.71 to 1.54)	160 per 1000	8 more per 1000 (from 46 fewer to 86 more)
PE	526 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.33 (0.03 to 3.18)	11 per 1000	8 fewer per 1000 (from 46 fewer to 86 more)
Major bleeding	713 (1 study) 14 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.59 (0.17 to 2)	19 per 1000	8 fewer per 1000 (from 16 fewer to 19 more)
PE, fatal	526 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 1.00 (0.06 to 16.03)	4 per 1000	0 fewer per 1000 (from 4 fewer to 54 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 91: Clinical evidence summary: LMWH (high dose; standard duration) versus LMWH (standard dose; standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (standard dose)	Risk difference with LMWH (high dose) (95% CI)
All-cause mortality	91 (1 study) 14 days	LOW[a] due to imprecision	Peto OR 0.13 (0 to 6.67)	22 per 1000	19 fewer per 1000 (from 22 fewer to 109 more)
Major bleeding	91 (1 study)	LOW[a] due to imprecision	Not estimable[b]	Not estimable[b]	0 fewer per 1000 (from 40 fewer to 40 more)[b]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (standard dose)	Risk difference with LMWH (high dose) (95% CI)
	14 days				
Heparin-induced thrombocytopenia	91 (1 study) 14 days	LOW[a] due to imprecision	Not estimable[b]	Not estimable[b]	0 fewer per 1000 (from 40 fewer to 40 more)[b]

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
b Zero events in both arms. Risk difference calculated in Review Manager.

Table 92:   Clinical evidence summary: LMWH (standard dose; standard duration) versus LMWH (low dose; standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (low dose)	Risk difference with LMWH (standard dose) (95% CI)
All-cause mortality	711 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.78 (0.53 to 1.15)	145 per 1000	32 fewer per 1000 (from 68 fewer to 22 more)
DVT (symptomatic and asymptomatic)	535 (1 study) 110 days	LOW[a,b] due to risk of bias, indirectness	RR 0.37 (0.22 to 0.64)	167 per 1000	105 fewer per 1000 (from 60 fewer to 130 fewer)
PE	535 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.13 (0.00 to 6.59)	4 per 1000	3 fewer per 1000 (from 4 fewer to 21 more)
Major bleeding	711 (1 study) 14 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 5.85 (0.71 to 48.34)	3 per 1000	14 more per 1000 (from 1 fewer to 135 more)
PE, fatal	535 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 1.89 (0.20 to 18.23)	4 per 1000	3 more per 1000 (from 3 fewer to 61 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (low dose)	Risk difference with LMWH (standard dose) (95% CI)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 93: Clinical evidence summary: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (standard duration)	Risk difference with LMWH (extended duration) (95% CI)
All-cause mortality	4335 (1 study) 90 days	LOW[a,b] due to risk of bias, imprecision	RR 1.01 (0.77 to 1.31)	48 per 1000	0 more per 1000 (from 11 fewer to 15 more)
PE	3685 (1 study) 90 days	VERY LOW[b] due to risk of bias, imprecision	RR 0.44 (0.11 to 1.7)	4 per 1000	2 fewer per 1000 (from 3 fewer to 3 more)
PE, fatal	3685 (1 study) 90 days	VERY LOW[b] due to risk of bias, imprecision	Peto OR 0.14 (0.11 to 1.7)	1 per 1000	1 fewer per 1000 (from 1 fewer to 1 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 94: Clinical evidence summary: LMWH (standard dose; standard duration) + AES versus AES

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with LMWH + AES (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with LMWH + AES (95% CI)
All-cause mortality	8307 (1 study) 90 days	HIGH	RR 0.97 (0.84 to 1.12)	86 per 1000	3 fewer per 1000 (from 14 fewer to 10 more)
Major bleeding	8307 (1 study) 8 days	LOW[a] due to imprecision	RR 1.44 (0.67 to 3.10)	3 per 1000	1 more per 1000 (from 1 fewer to 6 more)
Clinically relevant non-major bleeding	8307 (1 study) 8 days	LOW[a] due to imprecision	RR 1.27 (0.63 to 2.56)	3 per 1000	1 more per 1000 (from 1 fewer to 5 more)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 95: Clinical evidence summary: LMWH (standard dose; standard duration) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH	Risk difference with LMWH (95% CI)
All-cause mortality	6496 (5 studies) 8 - 90 days	VERY LOW[a,b,d] due to risk of bias, inconsistency, imprecision	RR 0.93 (0.59 to 1.45)	37 per 1000	3 fewer per 1000 (from 15 fewer to 17 more)
DVT (symptomatic and asymptomatic)	1539 (3 studies) 8 - 90 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 0.57 (0.37 to 0.87)	65 per 1000	28 fewer per 1000 (from 8 fewer to 41 fewer)
PE	6066 (5 studies) 8 - 90 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 0.73 (0.31 to 1.73)	4 per 1000	1 fewer per 1000 (from 3 fewer to 3 more)
Major bleeding	6545 (5 studies) 8 - 90 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 0.64 (0.33 to 1.23)	8 per 1000	3 fewer per 1000 (from 5 fewer to 2 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH	Risk difference with LMWH (95% CI)
PE, fatal	2041 (2 studies) not reported	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	Peto OR 0.92 (0.06 to 14.82)	1 per 1000	0 fewer per 1000 (from 1 fewer to 14 more)
Heparin-induced thrombocytopenia	3666 (2 studies) 90 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	Peto OR 0.31 (0.05 to 1.79)	2 per 1000	2 fewer per 1000 (from 2 fewer to 2 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 96: Clinical evidence summary: LMWH (standard dose; standard duration) versus apixaban

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Apixaban	Risk difference with LMWH (95% CI)
All-cause mortality	6528 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.49 (0.25 to 8.92)	1 per 1000	0 more per 1000 (from 0 fewer to 5 more)
PE	6517 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.14 (0.41 to 3.13)	2 per 1000	0 more per 1000 (from 1 fewer to 5 more)
Major bleeding (including fatal bleeding)	6401 (1 study) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.4 (0.15 to 1.02)	5 per 1000	3 fewer per 1000 (from 4 fewer to 0 more)
Major plus clinically relevant non-major bleeding	6401 (1 study)	LOW[a,b] due to risk of bias,	RR 0.78 (0.57 to	27 per 1000	6 fewer per 1000 (from 11 fewer to 2 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Apixaban	Risk difference with LMWH (95% CI)
	30 days	imprecision	1.07)		

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 97: Clinical evidence summary: Rivaroxaban versus LMWH (standard dose; standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH	Risk difference with Rivaroxaban (95% CI)
All-cause mortality	6265 (1 study) 35 days	MODERATE[a] due to imprecision	RR 1.06 (0.86 to 1.32)	48 per 1000	3 more per 1000 (from 7 fewer to 15 more)
DVT (symptomatic and asymptomatic)	6024 (1 study) 35 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.81 (0.64 to 1.02)	48 per 1000	9 fewer per 1000 (from 17 fewer to 1 more)
PE	6024 (1 study) 35 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.74 (0.33 to 1.65)	5 per 1000	1 fewer per 1000 (from 3 fewer to 3 more)
Major bleeding	7998 (1 study) 35 days	HIGH	RR 3.07 (1.68 to 5.61)	3 per 1000	7 more per 1000 (from 2 more to 16 more)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 98: Clinical evidence summary: Fondaparinux versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with Fondaparinux (95% CI)
All-cause mortality	839 (1 study) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.55 (0.29 to 1.03)	60 per 1000	27 fewer per 1000 (from 43 fewer to 2 more)
DVT (symptomatic and asymptomatic)	644 (1 study) 15 days	LOW[a,b] due to risk of bias, imprecision	RR 0.62 (0.35 to 1.1)	90 per 1000	34 fewer per 1000 (from 58 fewer to 9 more)
PE	839 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.24 (0.03 to 2.17)	10 per 1000	7 fewer per 1000 (from 9 fewer to 11 more)
Major bleeding	839 (1 study) 15 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.97 (0.06 to 15.60)	2 per 1000	0 fewer per 1000 (from 2 fewer to 34 more)
PE, fatal	839 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.42 (0.11 to 1.6)	17 per 1000	10 fewer per 1000 (from 15 fewer to 10 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

16.4 Economic evidence

Published literature

An original model was developed in CG92 for this question and is included here.[124] Additionally, two health economic studies were identified with the relevant comparison and have been included in this review. [115,199] These are summarised in the health economic evidence profiles below (Table 99, Table 100 and Table 101) and the health economic evidence tables in appendix J.

See also the health economic study selection flow chart in appendix F.

Table 99: **Health economic evidence profile: LMWH (standard dose, standard duration), UFH (standard duration), Fondaparinux (standard duration) vs no prophylaxis**

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
National Guideline Centre 2010[124] ([UK])	Directly applicable [a]	Potentially serious limitations [b]	**-Study design:** CUA using decision analytic model based on NMAs **-Population:** Adult (18 years or older) admitted as general medical admissions to hospitals in England. **-Interventions:** 1. No prophylaxis 2. LMWH (average of dalteparin 5000 units subcutaneously daily) and enoxaparin (4000 units subcutaneously daily) 3. UFH (5000 units three times daily) 4. Fondaparinux sodium (2.5 mg subcutaneously daily)	NR	NR	**Incremental net monetary benefit (INMB):** No prophylaxis: £0 LMWH: £328 UFH: £118 Fondaparinux: -£61	None of the sensitivity analyses undertaken changed the most cost-effective strategy except where the baseline risk of PE is very low and that of MB is increased, where the strategy of no prophylaxis becomes the most cost-effective strategy.

Abbreviations: CUA: cost-utility analysis; DVT: deep vein thrombosis; ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; LMWH: low molecular weight heparin; MB: major bleeding; NMA: network meta-analysis; PE: pulmonary embolism; QALY: quality-adjusted life years; RCT: randomised controlled trial; UFH: unfractionated heparin; VTE: venous thromboembolism.

(a) Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context.

(b) The relative treatment effect applied to all VTE events in the model is the relative treatment effect obtained from the DVT NMA.

Table 100: Health economic evidence profile: LMWH (standard dose, standard duration) vs no prophylaxis

Study	Applicability	Limitations	Other comments	Cost	Effects	Incremental costs	Incremental effects	Cost effectiveness	Uncertainty
Millar 2016 [115] ([Australia])	Partially applicable[a]	Potentially serious limitations [b]	**-Study design:** Cost-consequences analysis using decision tree model based on the results of a single RCT (the PREVENT trial) **-Population:** adult internal medicine patients admitted to all Australian hospitals **-Interventions:** 1. No prophylaxis 2. VTE prophylaxis using LMWH (Enoxaparin 40 mg/day). Three levels of eligibility for prophylaxis were examined: 2.a. restricted[d] (25% of all admissions), 2.b. intermediate[c] (40% of all admissions) and 2.c. broad[e] (80% of all admissions)	1. £29	1. 4.3 DVTs, 2.3 PEs, 0.4 deaths per 1000	DVT: No prophylaxis: dominated Restricted eligibility: baseline Intermediate eligibility: extendedly dominated Broad eligibility: £29,861 per DVT averted			A range of sensitivity analyses were conducted including changing baseline VTE risk, fatality rate for PE and major bleeding and assumptions regarding VTE risk in non-eligible patients.
				2.a. £26	2.a. 2.5 DVTs, 2 PEs, 0.5 deaths per 1000	PE: No prophylaxis: dominated Restricted eligibility: baseline Intermediate eligibility: extendedly dominated Broad eligibility: £170,827 per DVT averted			
				2.b. £30	2.b. 2.4 DVTs, 1.99 PE, 0.6 deaths	Deaths: No prophylaxis: £30,000 per death averted Restricted eligibility: baseline Intermediate eligibility: dominated Broad eligibility: dominated			
				2.c. £39	2.c. 2.1 DVTs, 1.93 PEs, 0.9 deaths per 1000				

Abbreviations: DVT: deep vein thrombosis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; PE: pulmonary embolism; QALY: quality-adjusted life years; RCT: randomised controlled trial; VTE: venous thromboembolism.

(a) Some uncertainty regarding the applicability of resource use and cost data from Australia in 2014 to current NHS context. Discounting was used only for health outcomes and the rate used is different from that recommended in the NICE Reference Case. QALYs are not used as an outcome measure.

(b) The model has a short time horizon that covers only the duration of the hospital stay, hence, does not capture long term costs. Only symptomatic events are included in the model. The source of baseline risk and relative treatment effects is based on a single trial and is not reflective of the total body of evidence. The results of the costs and outcomes are not presented as means per patient.

(c) Restricted: where only patients with strongest risk factors were given prophylaxis (malignancy, especially with chemotherapy, previous history of VTE, some rarer high risk conditions such as inflammatory bowel disease. (~ 25% of all inpatient admissions)

(d) Intermediate: where patients with strong and moderate risk factors, such as cardiac or respiratory failure, sepsis or inflammation, are given prophylaxis (~ 40% of all inpatient admissions)

(e) Broad: where everyone from the intermediate group as well as those satisfying an age criterion (>40 or >60) are given prophylaxis (~80% of all inpatient admissions)

Table 101: Health economic evidence profile: LMWH (standard dose, standard duration) vs UFH (standard duration)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Wilbur 2011[199] ([Canada])	Partially applicable[a]	Potentially serious limitations[b]	**-Study design:** Cost-consequences analysis using decision tree model **-Population**: Hypothetical cohort of adult internal medicine patients. Results were reported separately for the cancer subgroup **-Interventions:** 1. UFH (5000 U, twice daily [bid], SC]) initiated on day 1 of hospital stay and continued for 7 days 2. LMWH (enoxaparin 40 mg, once daily [od], administered subcutaneously [SC]) initiated on day 1 of hospital stay and continued for 7 days	**2 vs 1:** £4 **Cancer subgroup** 2 vs 1: £2	**2 vs 1:** 3 **less** True DVT events per 1000 1.3 **less** untoward events (PE, major bleeding and death) per 1000 **Cancer subgroup:** 2 vs 1: 6 **less** True DVT events per 1000 7 **less** untoward events (PE, major bleeding	**ICER:** £1,116 per DVT averted £3,726 per untoward event averted **Cancer subgroup:** ICER: £287 per DVT averted £1,037 per untoward event averted	Wide range of one-way sensitivity analyses was conducted. Overall, the results were consistent across the different scenarios considered.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
					and death) per 1000		

Abbreviations: DVT: deep vein thrombosis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; PE: pulmonary embolism; QALY: quality-adjusted life years; RCT: randomised controlled trial; VTE: venous thromboembolism.

(a) *Some uncertainty regarding the applicability of resource use and cost data from Canada in 2009 to current NHS context. The perspective used was that of the institution. QALYs are not used as an outcome measure.*

(b) *The model has a short time horizon that covers only the duration of the hospital stay (7 days), hence, does not capture long term costs and effects. The main outcome reported (untoward events) is a composite outcome measure and its use would underestimate the rate of these events as the occurrence of multiple events is counted as one event. The source of baseline risk and relative treatment effects is slightly outdated. Unit costs are based on both national and local sources and it is not clear if the local sources are reflective of national unit costs. The results of the sensitivity analysis were not reported for the cancer subgroup.*

16.5 Evidence statements

Clinical

LMWH at a standard dose for a standard duration was compared with no prophylaxis, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE, heparin-induced thrombocytopenia and clinically relevant non-major bleeding were reported across four studies. There was clinical benefit of LMWH in terms of all-cause mortality and DVT (symptomatic and asymptomatic), although the mortality outcome was also consistent with no difference. There was possible clinical benefit in terms of PE, fatal PE and heparin-induced thrombocytopenia, although there was considerable uncertainty around these results. There was possible clinical harm in terms of major bleeding and clinically relevant non-major bleeding, however there was also considerable uncertainty around these results. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

LMWH at a high dose for a standard duration was compared with no prophylaxis, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic) and fatal PE were reported in one study. There was possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic) and fatal PE and no clinical difference in terms of all-cause mortality, however the considerable uncertainty around these results meant that they could in fact be consistent with harm, no difference and benefit. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

LMWH at a low dose for a standard duration was compared with no prophylaxis, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and fatal PE were reported in one study. There was possible clinical benefit of LMWH in terms of PE and major bleeding, although the confidence intervals around these estimates were very imprecise. There was possible clinical harm in terms of all-cause mortality and no clinical difference in terms of DVT (symptomatic and asymptomatic) and fatal PE, although again there was considerable uncertainty around these results. The quality of the evidence was very low due to risk of bias, indirectness and imprecision.

LMWH at a high dose for a standard duration was compared with LMWH at a standard dose at a standard duration, the outcomes all-cause mortality, major bleeding and heparin-induced thrombocytopenia were reported in one study. There was possible clinical benefit of LMWH in terms of all-cause mortality and no clinical difference in terms of major bleeding and heparin-induced thrombocytopenia. However there was considerable uncertainty around all these results. The quality of the evidence was low due to imprecision.

LMWH at a standard dose for a standard duration was compared with LMWH at a low dose at a standard duration, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and fatal PE were reported in one study. Low quality evidence showed clinical benefit of LMWH at a standard dose for DVT (symptomatic and asymptomatic). Very low quality evidence suggested possible clinical benefit of LMWH at a standard dose in terms of all-cause mortality and PE. There was possible clinical harm of LMWH at a standard dose in terms of major bleeding and fatal PE. However for these four outcomes there was considerable uncertainty around the results. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

LMWH at a standard dose for an extended duration was compared with LMWH at a standard dose for a standard duration, the outcomes all-cause mortality, PE and fatal PE were reported in one

study. There was possible clinical benefit of LMWH for an extended duration in terms of PE and fatal PE, but these results were also consistent with both no difference and possible harm when considering their uncertainty. There was no clinical difference in terms of all-cause mortality. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration in combination with AES was compared with AES alone, the outcomes all-cause mortality, major bleeding and clinically relevant non-major bleeding were reported in one study. There was a suggested clinical benefit of LMWH in combination with AES in terms of all-cause mortality, however this finding was also consistent with no difference. There was possible clinical harm of LMWH in combination with AES in terms of major bleeding and clinically relevant non-major bleeding, however there was very serious imprecision around both of these results. The quality of the evidence ranged from low to high due to imprecision. The outcome with high quality evidence was all-cause mortality.

LMWH at a standard dose for a standard duration was compared with UFH, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE and heparin-induced thrombocytopenia were reported across five studies. There was possible clinical benefit of LMWH in terms of all-cause mortality, DVT (symptomatic and asymptomatic), major bleeding, heparin-induced thrombocytopenia. However the uncertainty around these results was also consistent with no difference and in some cases clinical harm (all cause mortality and HIT). There was no clinical difference in terms of PE and fatal PE, however there was also uncertainty around these results. The quality of the evidence was very low due to risk of bias, indirectness, imprecision and inconsistency.

LMWH at a standard dose for a standard duration was compared with apixaban, the outcomes all-cause mortality, PE and major bleeding were reported in one study. There was possible clinical benefit of LMWH in terms of major bleeding, however the imprecision around this result may also have been consistent with no difference. There was no clinical difference in terms of all-cause mortality and PE, but the imprecision around these results showed consistency with both possible benefit and harm. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

Rivaroxaban was compared with LMWH at a standard dose for a standard duration, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and major bleeding were reported in one study. There was possible clinical benefit of rivaroxaban in terms of PE, however the uncertainty around this result was also consistent with no difference or harm. High quality evidence showed clinical harm of rivaroxaban in terms of major bleeding, Moderate quality evidence suggested possible clinical harm in terms of all-cause mortality, although this finding was also consistent with no difference. There was no clinical difference in terms of DVT (symptomatic and asymptomatic). The quality of the evidence ranged from very low to high due to risk of bias, indirectness and imprecision. The outcome with high quality evidence was major bleeding.

Fondaparinux was compared with no prophylaxis, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and fatal PE were reported in one study. There was possible clinical benefit of fondaparinux in terms of all-cause mortality, DVT (symptomatic and asymptomatic), PE and fatal PE, however the uncertainty around these results were also consistent with no difference and in the case of the PE outcomes, also clinical harm. There was no clinical difference in terms of major bleeding, although this finding was also very uncertain. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

Economic

- One cost-utility analysis found that for VTE prophylaxis in general medical patients admitted to hospital the following interventions were cost-effective (having positive incremental net monetary benefit [INMB] compared to no prophylaxis: low molecular weight heparin (standard

dose, standard duration) (INMB: 328), unfractionated heparin (standard duration)(INMB: £118). The same analysis found that for VTE prophylaxis in general medical patients admitted to hospital fondaparinux sodium (standard duration) was not cost-effective compared to no prophylaxis (INMB: -£61). This analysis was assessed as directly applicable with potentially serious limitations.

- One cost-consequences analysis found that in general medical patients admitted to hospital:
  - Restricted eligibility to VTE prophylaxis (25% of all admissions) is less costly (£3 less per patient) and had 0.0018 fewer DVT events per patient and 0.0003 fewer PE events per patient but 0.0001 more deaths per patient compared to no prophylaxis.
  - Intermediate eligibility to VTE prophylaxis (40% of all admissions) is more costly (£1 more per patient) and had 0.0019 fewer DVT events per patient and 0.0003 fewer PE events per patient but 0.0002 more deaths per patient compared to no prophylaxis.
  - Broad eligibility to VTE prophylaxis (80% of all admissions) is more costly (£10 more per patient) and had 0.0022 fewer DVT events per patient and 0.0004 fewer PE events per patient but 0.0005 more deaths per patient compared to no prophylaxis.

  This analysis was assessed as partially applicable with potentially serious limitations.

- One cost-consequences analysis found that for VTE prophylaxis:
  - In internal medicine patients admitted to hospital, low molecular weight heparin (standard dose, standard duration) was more costly (£4 more) and had 0.003 fewer DVT events per patient and 0.013 fewer untoward events (PE, major bleeding and death) per patient compared to unfractionated heparin (standard duration).
  - In the cancer patients sub group, low molecular weight heparin (standard dose, standard duration) was more costly (£2 more per patient) and had 0.006 fewer DVT events per patient and 0.007 fewer untoward events (PE, major bleeding and death) per patient compared to unfractionated heparin (standard duration).

  This analysis was assessed as partially applicable with potentially serious limitations.

16.6 Recommendations and link to evidence

Recommendations	**1.4.6 Offer pharmacological VTE prophylaxis for a minimum of 7 days to acutely ill medical patients whose risk of VTE outweighs their risk of bleeding:** • **Use low-molecular-weight heparin (LMWH)[qqq] as first-line treatment.** • **If LMWH[rrr] is contraindicated use fondaparinux sodium[sss]. [2018]** **1.4.7 If using pharmacological VTE prophylaxis for people with renal impairment choose either LMWH[ttt] or unfractionated heparin (UFH).**

[qqq] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[rrr] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[sss] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	[2018] **1.4.8 If needed, reduce the dose of LMWH**[uuu] **and UFH for people with renal impairment. Base the decision on multidisciplinary or senior opinion, or locally agreed protocols. [2018]**
Research recommendation	**None**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (up to 7–90 days from hospital discharge), pulmonary embolism (up to 7–90 days from hospital discharge), fatal PE (7–90 days from hospital discharge), and major bleeding (up to 45 days from hospital discharge) as critical outcomes.
	The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), heparin-induced thrombocytopenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.
	Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	Nineteen randomised controlled studies were included in this review. Nine of these studies were included in the previous guideline (CG92). Ten new studies were added to the review.
	Data from subgroup analyses following two of the included studies was included in the clinical evidence tables for information and was not analysed. One of the studies included had subgroup analyses evaluating people with cancer and health failure within the study population as well as the influence of age. The other study evaluated people with ischaemic stroke within the study population.
	Eleven comparisons were included in this review, evaluating the use of pharmacological (LMWH, UFH, apixaban, rivaroxaban and fondaparinux) and mechanical (AES) interventions for VTE prophylaxis. A majority of the studies evaluated the use of LMWH versus other pharmacological interventions.
	The committee noted that a number of studies failed to clearly define their outcomes or methods of ascertaining VTE events. This was particularly notable for the major bleeding outcome where many failed to clearly define this. The committee chose to include these papers and downgrade the evidence for indirectness of outcome.
	The committee noted that overall the quality of evidence was low due to an increased risk of bias across many studies and imprecision around the effect estimates.
Trade-off between	Overall, the committee considered that the clinically beneficial effects of LMWH and

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[ttt] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[uuu] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

clinical benefits and harms	fondaparinux were prominent enough to adopt the recommendation from CG92. The committee commented that the LMWHs that are more commonly used in practice in the acutely ill medical population are enoxaparin, dalteparin and tinzaparin. The committee also noted that a majority of the studies evaluated patients who are at higher risk of VTE, including older adults and people who are immobilised.
	The committee noted that DOACs offered equal benefit in reduction of VTE compared to LMWH, however they also led to an increased risk of major bleeding. The committee also noted that DOACs are not currently licenced for use in acutely ill medical patients. NICE policy states that off‑label use may be recommended if the clinical need cannot be met by a licensed product and there is sufficient evidence and/or experience of using the medicine to demonstrate its safety and efficacy to support this. As clinical need can be met by a licensed product (i.e. LMWH), DOACs were not recommended.
	The committee wished to highlight that there was no evidence for the effectiveness of mechanical prophylaxis in this population. Therefore given the size of this population and possible resource impact of recommending AES or IPCD which have no proven benefit, the committee decided not to make a recommendation about mechanical prophylaxis. For those contraindicated for pharmacological prophylaxis, the committee decided that the clinician must use clinical judgement to weigh the risk of VTE with the risk of bleeding, and for those with a high risk of bleeding or for those who may be contraindicated for pharmacological prophylaxis for other reasons, they did not feel they could recommend mechanical prophylaxis on the basis of no evidence.
Trade-off between net clinical effects and costs	Three economic studies were included for this review. One was the model from CG92 which compared LMWH (standard dose, standard duration), UFH (standard duration), fondaparinux (standard duration) to no prophylaxis. The second compared LMWH (standard dose, standard duration) to no prophylaxis and the third compared LMWH (standard dose, standard duration) to UFH (standard duration). The CG92 model was assessed as directly applicable while the other two studies were assessed as partially applicable. All three studies were assessed to have potentially serious limitations.
	The committee noted that there was potential for the DOACs to offer an advantage in this population given their effectiveness in relation to DVT and PE compared to LMWH (standard dose, standard duration), and their oral route of administration and lower acquisition cost; however; it was noted that they also had a much higher risk of bleeding, so it is not clear whether they would be cost-effective in this population. The committee noted that without a clear evidence of benefit, these DOACs would not be recommended for off-label use in this population.
	The committee discussed the evidence and noted the lack of good quality evidence to support the use of mechanical prophylaxis in this population despite its potential benefit from reducing the use of pharmacological prophylaxis, with its associated risk of bleeding, in this largely elderly and immobile population.
	The committee determined that the new evidence is in line with current practice (that largely followed the CG92 recommendation), to offer pharmacological prophylaxis for people assessed to be at higher risk of VTE and low risk of bleeding. Hence, the committee decided to adopt the CG92 recommendation. The committee discussed whether both LMWH and fondaparinux should be offered as options, given that fondaparinux was not cost-effective according to CG92 model, and decided that fondaparinux can be recommended only as an option if LMWH was contraindicated.
Other considerations	The committee commented on the broad terminology used in the previous guideline for this population – general medical patients. It is difficult to define this population as definitions can vary across hospital settings. The committee considered a more helpful term would be acutely ill medical patients (for example acute medical

admissions), but appreciated the fact that no matter what terminology is used this population is very mixed, presenting patients with different risks of developing VTE.

The committee discussed that there is a high prescription rate of pharmacological VTE prophylaxis within this population and thus discussed the crucial need for an appropriate risk tool that will effectively reduce the number of patients being given VTE prophylaxis when they are not highly at risk of VTE. The committee agreed it necessary to highlight the particular need for VTE risk assessment in this population to ensure that VTE prophylaxis is not over-prescribed.

The committee discussed the use of VTE prophylaxis in people with renal impairment (eGFR <30 ml/min). Based on the pharmacokinetics, manufacturer's licensing and known clinical practice, the committee determined that LMWH or unfractionated heparin would be the most appropriate options for prophylaxis in this population, rather than fondaparinux or oral anticoagulants because the risk of bleeding may be increased in the renal impairment population. Because of this, dose reduction of LMWH or UFH may be required. Unfractionated heparin may occasionally be preferred to LMWH as it has a shorter half life and it can be reversed with protamine. Additionally it does not usually require dose adjustment in patients with significant renal impairment . It may be preferred in patients where reversal may be required, for example if bleeding may occur or there may be a need for acute surgery.

The two recommendations for people with renal impairment will be cross-referred to from each of the different population chapters within the guideline.

17 People with cancer who are having day procedures

17.1 Introduction

Active cancer is an additional risk factor for VTE and the prothrombotic tendency varies with tumour type, stage and treatments such as chemotherapy. Furthermore, many surgical procedures are carried out as part of curative or palliative cancer treatment.

Whilst the increased bleeding risk of cancer patients receiving full anticoagulation is well recognised when compared to non-cancer patients, there has been no evidence identified suggesting this is the case with primary thromboprophylaxis. However, the studies reviewed excluded those at highest risk of bleeding. Based on the clinical evidence standard contraindications to VTE prophylaxis should apply to this group.

This chapter considers two populations:

- cancer patients admitted to hospital with an acute illness which may or may not be due to their cancer diagnosis
- cancer patients admitted to hospital for oncological treatment.

For patients with cancer who are undergoing surgery, refer to guidance provided for the specific types of surgery in chapters 9–18.

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

For full details see review protocol in appendix C.

Table 102: PICO characteristics of review question

Population	Adults and young people (16 years and older) with cancer 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:

	o enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)
	o 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*)
	o 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:
	o Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)
	o Certoparin (3000 units daily)
	o Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)
	o Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)
	o Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)
	• Vitamin K Antagonists:
	o warfarin (variable dose only)
	o acenocoumarol (all doses)
	o 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 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- 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 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.

17.3   Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of mechanical and pharmacological prophylaxis strategies (alone or in combination) in cancer patients attending hospital. A Cochrane review was identified; [49] however the review protocol differed slightly from the current review. The Cochrane review included papers with higher (non-prophylactic) doses, following patients who are not in a hospital setting, or the primary outcome was treatment-related (the intervention's effect on cancer survival) rather than VTE prophylaxis. Therefore the references were checked and those appropriate to our review protocol were included and the rest excluded.

Eight papers were included in the review, detailing 9 trials;[4, 66, 67, 96, 103, 104, 144, 151, 152] these are summarised in Table 103 below. One of these papers was included in the previous guideline. [103] Evidence from these studies is summarised in the clinical evidence summary section below. The included studies cover a diverse range of cancer populations with most of the included papers involve people coming into hospital for chemotherapy. The papers also did not always make it clear how many people in their studies had central venous catheters inserted. The evidence covers an extremely wide time-range for the duration that people are receiving VTE prophylaxis, from as short as 8 days to as long as 25 months. The duration has always been interpreted as "standard" where the VTE prophylaxis was given for the duration of chemotherapy. See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

Table 103:   Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Agnelli 2009 [4] Trial name: PROTECHT (Prophylaxis of Thromboembolism during	Intervention (n=799): LMWH, high dose, standard duration (nadroparin 3800U, once daily). Median duration 111 days. Comparison (n=387): no VTE prophylaxis	n=1166 People with metastatic or locally advanced lung, gastrointestinal (stomach, colon, or rectum), pancreatic, breast, ovarian, or head and neck cancer who were receiving	All-cause mortality (study treatment period – 120±10 days) DVT (study treatment period +10 days – 130±10 days, median 111-113 days)	CVC 41.9% in intervention group and 38.6% in control group.

Study	Intervention and comparison	Population	Outcomes	Comments
Chemotherapy); ClinicalTrials.gov Identifier:NCT00951574	(placebo, saline solution). Median duration 113 days Prophylaxis started on the day of chemotherapy and given for the duration of chemotherapy or a maximum of 120 days	chemotherapy Adults (>18 years; mean intervention 62.1±10.3, comparison 63.7±9.2) Males and females (555:595) 62 centres in Italy	PE (study treatment period +10 days – 130±10 days, median 111-113 days) Major bleeding (up to 48 hours after last injection): defined as fatal or clinically overt bleeding associated with a decrease in haemoglobin of at least 0.02g/mL over a 48 hour period, or with transfusion of two or more units of whole blood or red cells, or occurred in a critical organ (brain, spine, pericardium, retroperitoneum, or eye), or required invasive intervention	
Haas 2012 [67] Trial name: TOPIC-1	Intervention (n=174): LMWH, standard dose (certoparin 3000IU, once daily), Administered for 6 months Comparison (n=179): no VTE prophylaxis (placebo) Concurrent treatment: first- or second-line chemotherapy.	n=353 People with objectively proven, disseminated metastatic breast carcinoma, receiving first- or second-line chemotherapy Age mean (SD): intervention 54.6 (10.3), comparison 56.6 (11.0) Female Multicentre – 39 centres in Germany, Czech Republic, Ukraine, Romania and Belarus	All-cause mortality (for 6 months of prophylaxis) DVT (6 months): confirmed by ultrasound and/or venography PE (6 months): confirmed by CT ventilation perfusion scintigraphy Major bleeding (6 months): defined as bleeding that was fatal, retroperitoneal, intracranial, requiring transfusion of >2 units of packed red cells, or associated with a drop in haemoglobin of >20g/L Heparin-induced	

Study	Intervention and comparison	Population	Outcomes	Comments
			thrombocytopenia (6 months)	
Haas, 2012 [67] Trial name: TOPIC-2	Intervention (n=273): LMWH, standard dose (certoparin 3000IU, once daily) Administered for 6 months Comparison (n=274): No VTE prophylaxis (placebo) Concurrent treatment: first- or second-line chemotherapy.	n=547 People with objectively proven, inoperable disseminated primary non–small cell lung carcinoma of stage III or IV receiving standard first- or second-line chemotherapy Age mean (SD): intervention60.8 (9.5); comparison 60.3 (10.0) Males and females 454:92 Multicentre – 39 centres in Germany, Czech Republic, Ukraine, Romania and Belarus	All-cause mortality (6 months) DVT (6 months): confirmed by ultrasound and/or venography PE (6 months): confirmed by CT ventilation perfusion scintigraphy Major bleeding (6 months): defined as bleeding that was fatal, retroperitoneal, intracranial, requiring transfusion of >2 units of packed red cells, or associated with a drop in haemoglobin of >20g/L Heparin-induced thrombocytopenia (6 months)	
Larocca, 2012 [96]	Intervention (n=166): LMWH, standard dose, standard duration (enoxaparin 40mg once daily), Comparison (n=176): Aspirin (100mg, once daily) Prophylaxis was administered during the 4 cycles of radiation therapy and the 6 cycles of MPR consolidation. Median follow-up was 20 months. Concurrent	n=342 People with previously untreated, newly diagnosed multiple myeloma (NDMM) Age , median: For ASA and LMWH respectively - 57 and 58 (no range reported) Males and females: (186:156) 62 centres in Italy and Israel	DVT (6 months): symptomatic only PE (6 months): method of confirmation not reported Major bleeding (6 months): defined as fatal bleeding, symptomatic bleeding in a crucial area or organ, or bleeding that caused a reduction in haemoglobin concentration of >2g/dL or that necessitated transfusion of >2	A substudy of a phase 3, multicentre RCT to compare the efficacy and safety of ASA and LMWH, in preventing VTE in patients with MM treated with lenalidomide as first-line therapy

Study	Intervention and comparison	Population	Outcomes	Comments
	treatment was either consolidation regimen with melphalan-presnisone-lenalidominde (MPR) or standard high dose melphalan 200mg/m^2, followed by tandem stem cell transplantation in patients with newly diagnosed multiple myeloma		unites of whole blood or red blood cells	
Levine 1994 [103]	Intervention (n=154): VKA antagonist (warfarin, low dose, 1mg daily, PT was measured every 2 weeks and adjustments of the dose were made if PT exceeded a defined level. At 6 weeks, the warfarin dose was adjusted based on an INR of 1.3-1.9) Administered at the start of chemotherapy or within 4 weeks and continued until 1 week after termination of chemotherapy. Mean duration (SD) 199 (126) days. Comparison (n=161): no VTE prophylaxis (placebo). Mean duration (SD) 188 (137) days	n=315 People with metastatic breast carcinoma who had been receiving first or second line chemotherapy for 4 weeks or less Age, mean (SD): warfarin 57.1 (10.20); comparison 56.1 (10.9) Gender not reported Canada and Italy	All-cause mortality (time-point not reported) DVT (symptomatic only): not analysed PE (time-point not reported): confirmed by ventilation-perfusion lung scanning Major bleeding (time-point not reported): defined as a fall in haemoglobin concentration of 20g/L or more or a need for transfusion of two or more units of blood, o retroperitoneal or intracranial bleeding	Included in CG92 CVC 3.5%
Levine 2012 [104]	Intervention: Apixaban (combined 3 different dose populations): 5 mg (n=32), 10mg (n=30), 20mg (n=33) Comparison (n=30): no VTE prophylaxis	n=125 People receiving either first-line or second-line chemotherapy for advanced or metastatic lung, breast, GI (colon, rectum, pancreas, stomach), bladder,	All-cause mortality DVT (114-121 days – during treatment period): symptomatic only, confirmed by compression ultrasound or venography (not	This was a phase II trial – a dose-ranging/tolerability study

Study	Intervention and comparison	Population	Outcomes	Comments
	(placebo)

Duration: 4 tablets once daily for 12 weeks, beginning within 4 weeks of chemotherapy initiation. Median duration 84 days. Range 14-92 in apixaban group, 7-91 in placebo group.

Concurrent treatment: all patients received chemotherapy (every 1, 2, 3, or 4 weeks for 12 weeks) | cancer of unknown origin, ovarian or prostate cancer, myeloma or selected lymphomas

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).

Males and females (63:62)

Canada, USA; (6 sites in Canada and 8 in the USA) | analysed)

PE (114-121 days): confirmed by spiral CT or ventilation/ perfusion lung scan

Major bleeding (114-121 days): defined as 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

Clinically relevant non-major bleeding (114-121 days): defined as 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 | |
| Palumbo, 2011 [144] | Intervention 1 (n=224):
Aspirin, 100mg, once daily | n=667

Age - Median (IQR): For ASA, warfarin and LMWH (enoxaparin): 61 (55-66); 60 (54-66); | All-cause mortality (6 months): sudden, otherwise unexplained death (presumed to be a result of PE, acute | This was a substudy of two simultaneous chemotherapy phase III trials in previously |

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=221): LMWH, standard dose, standard duration (enoxaparin 40mg, once daily) Prophylaxis administered during the three 21-day cycles of induction therapy in younger patients and the first six of nine 22-day cycles in elderly patients Median follow-up time was 24.9 months; primary endpoint measured within 6 months and during entire follow-up	62 (55-66). Gender (M:F): 362:297 People with previously untreated myeloma receiving thalidomide-based regimens in both of the parent trials 84 centres in Italy	myocardial infarction, or stroke). DVT (6 months): symptomatic only, not analysed. PE, symptomatic (6 months) confirmed by high-probability lung scan, a diagnostic spiral CT, diagnostic pulmonary angiography, or diagnostic transoesophageal echocardiography. Major bleeding (6 months): 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.	untreated patients with myeloma[26, 143]. Only those using thalidomide-based regimens were assessed for eligibility for the substudy on antithrombotic prophylaxis. Also included a warfarin arm but this was not included as it was fixed dose (1.25mg/day orally) and review protocol states variable dose only.
Pelzer 2015 [151] CONKO-004 Trial	Intervention (n=160): LMWH enoxaparin at half therapeutic dosage. 1mg/kg body weight, once daily for patients with impaired kidney function or thrombocytopenia, and 0.5mg/kg for CTC stage II thrombocytopenia. For 3 months of chemotherapy. Comparison (n=152): No VTE prophylaxis Concurrent	n=312 People with histological or cytological pancreatic carcinoma, no previous radiotherapy or chemotherapy Age, median (range): Enoxaparin: 62 (32-81); observation: 63 (27-83) Gender (M:F): Enoxaparin: 91:69; observation: 94:58 Germany – multicentre	DVT (3 months): asymptomatic only, not analysed. PE (3 months): method of confirmation not reported Major bleeding (3 months): defined as short term decline of haemoglobin level (>2g/dL per 48 hours), the absence of other evidence (e.g. haemolysis) and/or the need for at least two units of	

Study	Intervention and comparison	Population	Outcomes	Comments
	treatment: all patients received chemotherapy on days 1 and 8, once every 3 weeks for 3 months. Then, patients without disease progression received further chemotherapy on days 1, 8 and 15, once every 4 weeks	(no. of centres not reported)	RBC in cases of confirmed blood loss and/or the clinical occurrence of serious haemorrhage in parenchyma, muscle or cerebrum	
Perry 2010 [152]	Intervention (n=): LMWH standard dose (dalteparin 5000U, once daily) Administered for 6 months (and up to a further 6 months) Comparison (n=): no VTE prophylaxis (saline placebo) Concurrent therapy with acetylsalicylic acid, non-steroidal anti-inflammatory drugs and dextran was permitted but discouraged	n=186 People with newly diagnosed, pathologically confirmed WHO Grade 3 or 4 malignant glioma who had completed surgery and were receiving ongoing treatment. Age >18 years Canada	All-cause mortality (6 months) DVT (6 months): symptomatic only (not analysed) confirmed by venography or compression ultrasound PE (6 months): confirmed by autopsy, ventilation/perfusion lung scan or pulmonary angiogram Major bleeding (6 and 12 months): defined as clinically overt bleeding and: a decrease in haemoglobin of 20 gm L^{-1} or more over a 48 hour period, bleeding leading to a transfusion of two or more units of packed red cells, retroperitoneal, intracranial, intraspinal, intraocular or pericardial bleeding documented by objective investigation or bleeding leading to an invasive	77% of the LMWH group and 78% of the control group had radiotherapy within the first month. 53% of dalteparin and 57% of placebo patients also had pre/peri operative prophylaxis – either UFH, LMWH, AES or a combination.

Study	Intervention and comparison	Population	Outcomes	Comments
			intervention or death	

Table 104: Clinical evidence summary: LMWH (standard dose) versus no VTE prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH (standard dose) versus no prophylaxis (95% CI)
All-cause mortality	1065 (3 studies) 6 months	LOW[a,b] due to risk of bias, imprecision	RR 1.04 (0.8 to 1.37)	145 per 1000	6 more per 1000 (from 29 fewer to 54 more)
DVT	1050 (3 studies) 6 months	LOW[a,b] due to risk of bias, imprecision	RR 0.6 (0.35 to 1.04)	61 per 1000	24 fewer per 1000 (from 40 fewer to 2 more)
PE	1362 (4 studies) 3-6 months	LOW[a,b] due to risk of bias, imprecision	RR 0.41 (0.15 to 1.1)	17 per 1000	10 fewer per 1000 (from 14 fewer to 2 more)
Major bleeding	1377 (4 studies) 3-6 months	LOW[a,b] due to risk of bias, imprecision	RR 1.94 (0.98 to 3.84)	11 per 1000	10 more per 1000 (from 0 fewer to 31 more)
Heparin induced thrombocytopenia	898 (2 studies) 3-6 months	MODERATE[a] due to risk of bias	Not estimable[d]	See comment[d]	0 fewer per 1000 (from 10 fewer to 10 more)[c]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Absolute difference calculated manually in RevMan
d Cannot be calculated due to zero events in both arms

Table 105: Clinical evidence summary: LMWH (high dose) versus no VTE prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH (high dose) versus no prophylaxis (95% CI)
All-cause mortality	1150 (1 study) 111-113 days	LOW[a] due to imprecision	RR 1.02 (0.57 to 1.83)	42 per 1000	1 more per 1000 (from 18 fewer to 35 more)
DVT	766 (1 study) 111-113 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.64 (0.3 to 1.35)	44 per 1000	16 fewer per 1000 (from 31 fewer to 15 more)
PE	766 (1 study) 111-113 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.54 (0.11 to 2.68)	11 per 1000	5 fewer per 1000 (from 10 fewer to 18 more)
Major bleeding	766 (1 study) 111-113 days	LOW[a,b] due to risk of bias, imprecision	Peto OR 4.72 (0.75 to 29.73)	0 per 1000	-[d]

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
d Absolute risk difference cannot be calculated due to zero events in the control arm

Table 106: Clinical evidence summary: LMWH (standard dose) versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH (standard dose) versus aspirin (95% CI)
All-cause mortality	781 (2 studies) 20-25 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1 (0.06 to 16.11)	2 per 1000	0 fewer per 1000 (from 2 fewer to 29 more)
PE	781 (2 studies) 20-25 months	LOW[a,c] due to risk of bias, indirectness	Peto OR 0.14 (0.03 to 0.61)	18 per 1000	15 fewer per 1000 (from 7 fewer to 17 fewer)
Major bleeding	781 (2 studies) 20-25 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 1.3)	7 per 1000	6 fewer per 1000 (from 7 fewer to 2 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

Table 107: Clinical evidence summary: Apixaban versus no VTE prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Apixaban (all doses) versus no prophylaxis (95% CI)
All-cause mortality	122 (1 study) 70 days	LOW[a] due to imprecision	Peto OR 0.09 (0.01 to 1.31)	69 per 1000	62 fewer per 1000 (from 68 fewer to 19 more)
PE	122		Peto OR	35 per 1000	35 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Apixaban (all doses) versus no prophylaxis (95% CI)
	(1 study) 70 days	LOW[a] due to imprecision	0.01 (0 to 1.49)		(from 35 fewer to 16 more)
Major bleeding	122 (1 study) 70 days	LOW[a] due to imprecision	Peto OR 0.58 (0.04 to 8.53)	35 per 1000	14 fewer per 1000 (from 34 fewer to 201 more)
CRNMB	122 (1 study) 70 days	VERY LOW[a,c] due to indirectness, imprecision	Peto OR 3.84 (0.37 to 39.51)	0 per 1000	_[b]

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b Absolute risk difference cannot be calculated due to zero events in the control arm
c Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

Table 108: Clinical evidence summary: VKA versus no VTE prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with VKA versus no prophylaxis (95% CI)
All-cause mortality	311 (1 study) 199 days	LOW[a,b] due to risk of bias, indirectness	RR 0.92 (0.77 to 1.1)	623 per 1000	50 fewer per 1000 (from 143 fewer to 62 more)
PE	311 (1 study) 199 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 1.05 (0.07 to 16.81)	6 per 1000	0 more per 1000 (from 6 fewer to 86 more)
Major bleeding	311		Peto OR	13 per 1000	6 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with VKA versus no prophylaxis (95% CI)
	(1 study) 199 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	0.53 (0.06 to 5.18)		(from 12 fewer to 51 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

17.4 Economic evidence

Published literature

One health economic study was identified with the relevant comparison and has been included in this review.[28] This is summarised in the health economic evidence profile below (Table 109) and the health economic evidence table in appendix J.

See also the health economic study selection flow chart in appendix F.

Table 109: Health economic evidence profile: LMWH (standard dose, standard duration) vs aspirin

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Chalayer 2016[28] ([France])	Partially applicable [a]	Potentially serious limitations[b]	**-Population:** Patients newly diagnosed with multiple myeloma treated with protocols including thalidomide **-Study design:** Decision analytic model. **-Interventions:** **Intervention 1:** Aspirin (100mg/day) for 3 months. **Intervention 2:** LMWH standard dose, standard duration) (Enoxaparin 40mg/day) for 6 months.	2 vs 1 £1,053	2 vs 1 -0.001 QALYs	2 vs 1 Dominated	None of the sensitivity analyses changed the conclusion regarding cost effectiveness.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years

(a) Some uncertainty regarding the applicability of unit costs from France in 2013 to current NHS context.

(b) The model does not incorporate any long-term consequences such as CTEPH or PTS. Baseline risk and relative treatment effects are based on a single open-label trial, so by definition, does not reflect all available evidence. Costs of LMWH administration might be underestimated.

17.5 Evidence statements

Clinical

When comparing LMWH with no prophylaxis the only possibly clinically important difference, identified by low quality evidence, was an increase in major bleeding when using standard dose LMWH, although this finding could also be consistent with no difference when taking uncertainty into account. Low quality evidence suggested a possible harm for all cause mortality (3 studies) and a possible benefit for LMWH with reduction in DVT (3 studies) and PE (4 studies), however there was uncertainty around these effects. There was no difference between the two for heparin-induced thrombocytopenia. Low quality evidence showed no difference between high dose LMWH and no prophylaxis for all-cause mortality and a possible clinical harm for high dose LMWH with respect to major bleeding. Very low quality evidence suggested a reduction in DVT and PE with high dose LMWH but there was considerable uncertainty around these results.

When comparing LMWH (standard dose) to aspirin, the only clinically important difference was a reduction in PE for LMWH (low quality, precise evidence). Very low quality evidence also suggested a benefit of LMWH over aspirin for major bleeding events and no difference between the two for all-cause mortality, however there was imprecision around these results.

No clinically important differences were seen between apixaban and no prophylaxis. Low quality evidence suggested a benefit for apixaban for all-cause mortality, PE and major bleeding but these were uncertain results. There was also no clinically importance difference in outcomes between VKA and no prophylaxis. A possible benefit was noted for all-cause mortality and major bleeding but these were also consistent with no difference.

Economic

One cost utility analysis showed that aspirin was dominant (more effective and less costly) compared to LMWH (standard dose, standard duration) in patients newly diagnosed with multiple myeloma and receiving chemotherapy. The study was assessed as partially applicable with potentially serious limitations.

17.6 Recommendations and link to evidence

Recommendations	**1.4.9 Do not offer VTE prophylaxis to people with cancer who are receiving cancer modifying treatments such as radiotherapy, chemotherapy or immunotherapy and who are mobile, except as outlined in recommendations 1.4.10 and 1.4.11, unless they are also at increased risk of VTE because of something other than the cancer. [2018]**
	1.4.10 Consider pharmacological VTE prophylaxis for people with myeloma who are receiving chemotherapy with thalidomide, pomalidomide or lenalidamide with steroids. Choose either:
	• **aspirin[vvv] (75 or 150 mg) or**

vvv   At the time of publication (March 2018), aspirin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	• **LMWH**www**. [2018]** **1.4.11 Consider pharmacological VTE prophylaxis with LMWH**xxx **for people with pancreatic cancer who are receiving chemotherapy. [2018]** **1.4.12 If giving VTE prophylaxis to people with cancer (see recommendations 1.4.10 and 1.4.11). continue for as long as they are receiving chemotherapy. [2018]**
Research recommendation	**None**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge), pulmonary embolism (up to 90 days from hospital discharge), fatal PE (up to 90 days from hospital discharge), and major bleeding (up to 45 days from hospital discharge) as critical outcomes. The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), heparin-induced thrombocytopenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail explaining prioritisation of the critical outcomes.
Quality of the clinical evidence	Evidence ranged from moderate to low quality. The majority of the evidence for LMWH, aspirin and VKA was at a high risk of bias due to incomplete outcome data with the studies commonly reporting higher rates of attrition than event rates and many studies stopping early due to insufficient recruitment to reach adequate power. Evidence for high dose LMWH, VKA, aspirin and apixaban was also downgraded for outcome indirectness as the method of confirmation of DVT and PE was unclear as well as the definition of bleeding outcomes. Evidence across all outcomes was downgraded further due to imprecision around the effect estimates.
Trade-off between clinical benefits and harms	The population covered in this chapter is a highly heterogeneous population, both in terms of the many different forms of cancer and the different levels of VTE risk associated with different cancers. Certain cancers are known to be more thrombotic, particularly pancreatic cancer, lung cancer and myeloma, compared to other forms of cancer (such as breast cancer or prostate cancer). In addition, the thrombogenicity increases in patients with distant metastases and varies according to the type of chemotherapy given and the number of cycles given. For the majority of the evidence identified in the different cancer populations included in this review, there was no clinically important difference between those receiving prophylaxis compared to those not receiving prophylaxis. Therefore the committee specifically made a "do not offer" recommendation because this recommendation applies to the majority of the population who have cancer and are coming into hospital to receive cancer modifying treatments (non-hospitalised

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www At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

xxx At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

patients receiving chemotherapy, radiotherapy or other treatments such as radiofrequency ablation [RFA] or embolisation). This recommendation therefore has an important health economic impact that needed highlighting with the "do not offer" recommendation rather than simply having the recommendations relating to the particular cancer populations for which VTE prophylaxis would be recommended.

Whilst the committee made a "do not routinely" recommendation, this does not preclude the use of primary prophylaxis in patients in whom clinicians feel to be at higher risk. This might include patients with a previous history of VTE, or known thrombophilia. However, it should be stressed that these suggestions have not been supported by RCT data. Furthermore, clinicians need to weigh up the potential downsides of thromboprophylaxis during chemotherapy since highly marrow suppressive regimes may render patients profoundly thrombocytopenic and at greater risk of bleeding. In addition, routine administration of an injectable medicine (LMWH) with no evidence-based benefit may be considered ethically challenging as well as having a health economic impact.

The committee made recommendations for two specific cancer populations for which clinicians might consider VTE prophylaxis. People with myeloma who are receiving thalidomide, lenalidomide or pomalidomide (for which 3 RCTs and an economic evaluation were identified) are at increased risk for VTE due to this specific cancer treatment. The committee agreed that this risk warranted a recommendation to consider prophylaxis in this population. The evidence was of low quality for a reduction in PE with LMWH compared to aspirin and very low quality for reduction in major bleeding events. An economic study using clinical data from one of the included clinical papers suggested that the clinical differences between the two treatments were small and the associated lower cost and increased QALY's of aspirin lead to this being the more cost-effective choice. As discussed in the next section on trade-off between net clinical effects and costs, the committee considered that the evidence allowed for a weak recommendation that gives clinicians room to exercise judgement on whether to offer VTE prophylaxis to people with myeloma and if so, the choice of either LMWH or aspirin.

Another group identified for a specific prophylaxis recommendation were those with pancreatic cancer. Epidemiological data strongly suggest that pancreatic cancer is especially thrombotic compared to other cancers and the committee determined that this warranted a recommendation to consider VTE prophylaxis in this population. As evidence was identified for only LMWH in this population, the committee decided that this was the preparation that clinicians might consider. The weak recommendation reflects the uncertainty of the evidence base in this population.

While the committee also acknowledged the increased thrombogenicity associated with lung cancer (based on epidemiological data and healthcare registries), fewer trial data which matched the protocol for this review were identified for inclusion. This population has a higher risk of bleeding which precludes routine thromboprophylaxis, and therefore the committee decided not to make specific recommendations for this population, but they are covered in the "do not offer" recommendation for most cancers, unless identified as at greater VTE risk based on other, non-cancer, factors.

Trade-off between net clinical effects and costs	One economic study was included for this review. This was assessed as partially applicable with potentially serious limitations. The study showed that aspirin, 100 mg per day, was cost-effective compared to LMWH (enoxaparin 40 mg per day) in people recently diagnosed with multiple myeloma and receiving chemotherapy. The probabilities for the DVT, PE and major bleeding outcomes in the hypothetical cohort were taken from a study included in the clinical review.[144] Aspirin was associated with a higher frequency of VTE events and major bleeding, however the authors interpret the benefit of LMWH on clinical outcomes as only slightly superior to

aspirin. Aspirin is significantly less expensive and associated with more QALYs which is important in the context of incurable disease (multiple myeloma population). No economic evidence was found for people with pancreatic cancer. No evidence was found for mechanical prophylaxis in either population.

The committee discussed the economic evaluation findings and noted that the study focused on people with multiple myeloma who started on thalidomide-based chemotherapy. The committee also noted that despite aspirin being more cost-effective, the difference between aspirin and LMWH was not highly significant. Additionally, LMWH was more clinically effective in relation to symptomatic DVTs and PE outcomes. Hence, the committee considered that it would be appropriate to allow the choice of either aspirin or LMWH to be based on clinical factors and other relevant considerations such as the presence of contraindication to either, or individual preference for a particular route of administration (oral versus parenteral). The committee also discussed the duration of prophylaxis and noted that the duration in the trial that informed the economic evaluation was 6 months, however this was for pragmatic reasons and it would be expected that the level of VTE risk will continue for the duration of receiving chemotherapy.

The committee acknowledged the fact that the level of VTE risk in people receiving oncological treatment will be highly dependent on whether the individual is ambulant. For people who are ambulant, prophylaxis is unlikely to be cost effective due to the low level of risk. For those who are assessed to be at high risk of VTE due to their reduced mobility, it was considered to be appropriate to consider pharmacological prophylaxis. It was not possible to recommend a mechanical prophylaxis option in this population due to the lack of evidence of clinical or cost effectiveness.

Other considerations	The committee agreed that VTE prophylaxis for people with cancer depended on their level of risk for VTE. The committee noted that although a risk for predicting VTE in people having cancer day procedures had been identified (Khorana score), they did not think that the tool was sufficiently accurate to recommend in clinical practice (see Chapter 5). The committee agreed that for people with cancer having day procedures VTE risk will vary according to risk factors identified in many VTE risk assessment tools for medical or surgical patients, as well as additional cancer-specific risk factors[19] such as:

- Cancer primary: for example those with lung cancer, upper GI, ovarian, haematological are at higher risk for VTE than those with breast and prostate cancer

- Stage of cancer: those with metastatic disease are at higher risk

- Type of chemotherapy: cisplatin, thalidomide and fluorouacil based regimes are particularly thrombogenic

The committee noted that the British Society of Haematology guideline[196] recommends aspirin for people who are at low risk of developing VTE, and LMWH for those with high risk. However the committee did not believe that the current data support such a prescriptive recommendation and preferred to offer clinicians the option of using LMWH or aspirin based on the available clinical and health economic evidence.

The committee noted that the dose used for aspirin in the evidence represented a non-standard dose for the UK at 100mg per day. Clinicians can decide whether to use 75mg or 150mg.

18 Central venous catheters

18.1 Introduction

Central venous catheters (CVCs) are commonly used in a wide variety of patients for indications such as monitoring of haemodynamics, administration of parenteral nutrition, blood products, chemotherapy, and infusion fluids. One important complication with the use of CVCs is catheter-related thrombosis (CRT), the majority of which are asymptomatic. These are of uncertain clinical significance, but CRT has been reported in adult patients with cancer to cause morbidities including pulmonary embolism and postphlebitic syndrome.

The type and location of the catheter is important. In adult patients with cancer, patient history of VTE and previous catheter insertions, inadequate position of CVC tip, left-sided CVC insertion and chest radiotherapy have been identified as significant risk factors for CRT.

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

For full details see review protocol in appendix C.

Table 110: PICO characteristics of review question

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:
	o enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*)
	o 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*)
	o 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:
	o Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)
	o Certoparin (3000 units daily)
	o Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)
	o Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)
	o Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)
	• Vitamin K Antagonists:
	o warfarin (variable dose only)
	o 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: • Each other • No VTE prophylaxis treatment • Placebo Within intervention (including same drug) comparisons, including: • Standard versus extended duration prophylaxis • Low versus high dose treatments of 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 fibringen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) • Pulmonary embolism (symptomatic and asymptomatic) (up to 90 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:** • 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

18.3 Clinical evidence

Six randomised controlled trials were included in the review. From the 12 studies that were previously included in the previous guideline (CG92), 4 studies were included in this review; 2 studies

were excluded as no relevant outcomes were reported (Brismar 1982[22]; Macoviak 1984 [107]), 1 study (Abdelkefi 2004[1]) was excluded as the population included a number of children, and 5 studies (Bern 2002[16]; Couban 2005[40]; Heaton 2002[74]; Mismetti 2001[118]; Young 2009[204]) were excluded as the intervention did not match the protocol. Two studies have been added in the update[45, 97].

These are summarised in **Table 111** below. Evidence from these studies is summarised in the clinical evidence summary below (**Table 112**, **Table 113**,

Table 114 and

Table 115). See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

One Cochrane review[5] was identified which looked at anticoagulation for people with cancer and central venous catheters. The review included studies which were included in the previous guideline (CG92). Two studies (De Cicco 2009[45]; Lavau-Denes 2013[97]) from the review have been included here.

Summary of included studies

Table 111: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes
De Cicco 2009[45]	Intervention 1 (n=150): Vitamin K antagonist - Acenocoumarol 1 mg/day for 3 days before and 8 days after CVC insertion. Intervention 2 (n=150): Low molecular weight heparin - Dalteparin 500 IU, 2 hours before CVC insertion and daily after for 8 days. Comparison (n=150): No VTE prophylaxis treatment	n=450 People with active cancer, having chemotherapy, with central venous catheters Adults (aged 18 years or over; mean 55±12) Male to female ratio 165:285 Italy	All-cause mortality (30 days) DVT, CVC-related (30 days): no definition reported Major bleeding (30 days): clinically overt bleeding associated with a decrease in haemoglobin level of at least 2 d/dL or requiring a transfusion of 2 or more units of packed red cells in any 24-hour period
Karthaus 2006 [88]	Intervention (n=294): LMWH – standard dose (Dalteparin), 5000IU injected subcutaneously 1/day Comparison (n=145): placebo Concomitant treatment: catheter flushing with unfractionated heparin (500 IU)/saline boluses were allowed during catheter use	n=439 People with cancer with central venous catheters Adults (mean intervention 55.2±12.91, comparison 57.4 ±12.72) Male to female ratio 42:58 48 centres from 12 countries	All-cause mortality (112 days) PE, catheter related (112 days): confirmed by: ventilation perfusion scan or spiral CT scan Major bleeding (112 days): as described by adjudication committee
Lavau-Denes	Intervention (n=141): Low	n=420	All-cause mortality (90 days)

Study	Intervention and comparison	Population	Outcomes
2013[97]	molecular weight heparin - dalteparine, nadroparine or enoxaprine administered subcutaneously at recommended doses for prevention, once daily. Comparison (n=137): no VTE prophylaxis treatment	People with cancer with central venous catheters Adults (mean age 60, range 21–85) Male to female ratio 243:164 France	DVT, CVC-related (90 days): confirmed by Doppler US and venography DVT, non-CVC-related (90 days): confirmed by Doppler US and venography PE (90 days): no definition reported
Monreal 1996 [119]	Intervention (n=17): LMWH – standard dose (Dalteparin), 2500IU subcutaneously 1/day Comparison (n=15): no VTE prophylaxis treatment	n=32 People with cancer with central venous catheters Adults (mean 54; range 27–77) Male to female ratio 17:15 Spain	All-cause mortality (90 days) DVT, asymptomatic or symptomatic, subclavian (90 days): confirmed by venography Major bleeding (90 days): haematoma requiring surgical intervention
Niers 2007 [136]	Intervention (n=56): LMWH – low dose (Dalteparin), 2850 antifactor Xa (antiFXa) units subcutaneously 1/day Comparison (n=57): placebo	n=113 People with haematologic malignancies requiring central venous catheters Adults (mean intervention 58±10, comparison 53±13) Male to female ratio 62:51 The Netherlands	Major bleeding (21 days): overt bleeding with a fall in haemoglobin of 2 g/dL or more, or leading to a transfusion of 2 or more units of packed red blood cells or bleeding in a critical organ such as intracranial, retroperitoneal or pericardial bleeding, or contributing to death Clinical relevant non-major bleeding (21 days): overt bleeding not meeting the criteria for major bleeding, and included skin haematoma if the size was larger than 100 cm² 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

Study	Intervention and comparison	Population	Outcomes
			Heparin induced thrombocytopenia (21 days): clinical suspicion and positive antibodies against the heparin-platelet FIV complex
Verso 2005 [191]	Intervention (n=191): LMWH – standard dose (Enoxaparin) 40mg injection subcutaneously once per day. Start time: 2 hours prior to CVC insertion. Duration: 42 days ±2 days. Comparison (n=194): placebo. Start time: 2 hours prior to CVC insertion. Duration: 42 days ±2 days	n=385 People with cancer with central venous catheter Adults (≥18 years; mean intervention 59.1±11.9, comparison 59.5±12.4) Male to female ratio 176:209 Italy	All-cause mortality (90 days) PE, fatal (90 days): confirmed by autopsy DVT, symptomatic or asymptomatic, upper limb (90 days): confirmed by venography Major bleeding (90 days): decrease in haemoglobin level of at least 2 g/dL or requiring a transfusion of two or more units of packed red cells. Intracranial, retroperitoneal, and intraocular bleeding and bleeding requiring surgical intervention

Table 112: Clinical evidence summary: LMWH (standard dose; standard duration) versus no VTE prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no VTE prophylaxis	Risk difference with LMWH (standard dose) (95% CI)
All-cause mortality	1349 (5 studies) 30–112 days	VERY LOW[a,b,c,e] due to risk of bias, inconsistency, imprecision	RR 0.82 (0.51 to 1.32)	57 per 1000	10 fewer per 1000 (from 28 fewer to 18 more)
DVT	517 (2 studies) 30–90 days	VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision	RR 0.65 (0.5 to 0.85)	349 per 1000	122 fewer per 1000 (from 52 fewer to 175 fewer)
PE	712 (2 studies) 90–112 days	VERY LOW[a,c] due to risk of bias, imprecision	Peto OR 0.69 (0.04 to 11.98)	4 per 1000	1 fewer per 1000 (from 3 fewer to 38 more)
PE, fatal	385 (1 study) 90 days	VERY LOW[a,c] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 10 fewer to 10 more)[d]
Major bleeding	1193 (5 studies) 30–112	VERY LOW[a,b,c,e] due to risk of bias, inconsistency, indirectness, imprecision	Peto OR 1.14 (0.11 to 12.13)	2 per 1000	0 more per 1000 (from 2 fewer to 21 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Zero events in both arms. Risk difference calculated in Review Manager.
e The majority of the evidence had indirect outcomes

Table 113: Clinical evidence summary: LMWH (low prophylactic dose) versus no VTE prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no VTE prophylaxis	Risk difference with LMWH (low dose) (95% CI)
Major bleeding	113 (1 study) 21 days	VERY LOW[b,c] due to risk of bias, imprecision	Not estimable[a]	Not estimable[a]	0 fewer per 1000 (from 30 fewer to 30 more)[a]
Clinically relevant non-major bleeding	113 (1 study) 21 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[a]	Not estimable[a]	0 fewer per 1000 (from 30 fewer to 30 more)[a]
Heparin-induced thrombocytopenia	113 (1 study) 21 days	VERY LOW[b,c] due to risk of bias, imprecision	Not estimable[a]	Not estimable[a]	0 fewer per 1000 (from 30 fewer to 30 more)[a]

a Zero events in both arms. Risk difference calculated in Review Manager.
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 114: Clinical evidence summary: VKA versus no VTE prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no VTE prophylaxis	Risk difference with VKA (95% CI)
All-cause mortality	228 (1 study) 30 days	VERY LOW[a,c] due to risk of bias, imprecision	RR 1.27 (0.6 to 2.68)	96 per 1000	26 more per 1000 (from 39 fewer to 162 more)
DVT	228 (1 study) 30 days	LOW[a,b] due to risk of bias, indirectness	RR 0.39 (0.28 to 0.55)	526 per 1000	321 fewer per 1000 (from 237 fewer to 379 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no VTE prophylaxis	Risk difference with VKA (95% CI)
Major bleeding	228 (1 study) 30 days	VERY LOW[a,c] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 20 fewer to 20 more)[d]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Zero events in both arms. Risk difference calculated in Review Manager.

Table 115: Clinical evidence summary: LMWH (standard prophylactic dose) versus VKA

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with LMWH (standard dose) (95% CI)
All-cause mortality	234 (1 study) 30 weeks	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.81 (0.39 to 1.68)	123 per 1000	23 fewer per 1000 (from 75 fewer to 84 more)
DVT	234 (1 study) 30 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.82 (1.21 to 2.75)	219 per 1000	180 more per 1000 (from 46 more to 384 more)
Major bleeding	234 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 20 fewer to 20 more)[d]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with LMWH (standard dose) (95% CI)
c Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes					
d Zero events in both arms. Risk difference calculated in Review Manager.					

18.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

18.5 Evidence statements

Clinical

Very low quality evidence for the five critical outcomes was found in five studies comparing LMWH (standard prophylactic dose) with no prophylaxis. A possible clinical benefit of LMWH (standard prophylactic dose) was found with regards to all-cause mortality and DVT, however there was large imprecision around these effects meaning the findings could also be consistent with no difference, or in the case of mortality also consistent with possible harm. There was no difference for PE, fatal PE or major bleeding. The evidence was at a serious risk of bias for all outcomes and some inconsistency was noted in the mortality and major bleeding outcomes that could not be explained through subgrouping.

One study (n=113) compared LMWH (low prophylactic dose) with no prophylaxis and found no clinical difference with regards to major bleeding, clinically relevant major bleeding and heparin-induced thrombocytopenia. All of the evidence was of very low quality due to risk of bias and imprecision around the effect estimates.

One study (n=228) compared VKA (acenocoumarol 1 mg/day) with no prophylaxis. A clinically important benefit was found for VKA with regards to reduction in DVTs. However a possible clinical harm of VKA was found for all-cause mortality but this was of very serious imprecision and consistent with a clinical benefit and no clinical difference. No clinical difference was found with regards to major bleeding.

One study (n=234) compared LMWH (standard prophylactic dose) with VKA. With regards to a reduction in all-cause mortality very low quality evidence favoured LMWH over VKA, however this was of very serious imprecision and so was consistent with clinical harm and no clinical difference. With regards to DVT reduction very low quality evidence favoured LMWH over VKA, but again, this was of serious imprecision and so was consistent with no clinical benefit. No clinical difference was found with regards to major bleeding.

Economic

No relevant economic evaluations were identified.

18.6 Recommendations and link to evidence

Recommendations	None
Research recommendation	3. **What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for people with central venous catheters?**
Relative values of	The committee considered all-cause mortality (up to 90 days from hospital

different outcomes	discharge), deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge), pulmonary embolism (symptomatic and asymptomatic) (up to 90 days from hospital discharge), fatal PE (up to 90 days from hospital discharge), and major bleeding (up to 45 days from hospital discharge) as critical outcomes.
	The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), heparin-induced thrombocytopenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.
	Please see section 4.4.3 in the methods chapter for further detail explaining prioritisation of the critical outcomes.
Quality of the clinical evidence	People with central venous catheters without cancer
	The committee noted an absence of evidence for people with CVC who do not have cancer, for example people with sickle cell disease, recurrent transfusions or having nutrition support.
	People with central venous catheters with cancer
	Six randomised controlled trials were included in the review, which were all conducted in a population of people with CVCs who have cancer, and are also assumed to be undertaking chemotherapy. All of the evidence was of low to very low quality, with the majority being of very low quality. All of the evidence was of serious to very serious risk of bias. The majority of the evidence was consistent, apart from some outcomes in the LMWH (standard prophylactic dose) versus no VTE prophylaxis comparison. Some of the outcomes were downgraded for indirectness where the method of confirmation or time point when the outcome was measured was different to that specified in the protocol, or where the method was not reported. The majority of evidence was also very seriously imprecise, where the data are consistent with a clinical benefit, harm or no clinical difference.
Trade-off between clinical benefits and harms	The committee noted that many of the included papers were over five years old and data may be less transferable to current practice. The presence of a CVC in patients with cancer may predispose the person to upper extremity DVT precipitated by the chemotherapy and thrombogenicity associated with certain types of cancer. People without cancer using CVCs are usually receiving antibiotics or parenteral nutrition. The thrombotic state in this population may be related to the CVC causing some endothelial damage and turbulent flow at the tip of the line. However, newer CVC lines with lower thrombogenicity are now used and greater emphasis has been given to ensure optimal catheter tip placement. Therefore, given increased improvements in CVC technology and as there was no evidence identified in people without cancer who have CVC, the committee decided not to make a recommendation for this population.
	The majority of the evidence identified was for LMWH and the committee did not consider that the evidence for VKA was strong enough to add VKA as a prophylaxis option. Therefore the committee determined that LMWH was the best option for clinicians to consider, based on the suggested reductions in DVT and all-cause mortality and no difference in bleeding events. A 'consider' recommendation was deemed most appropriate, reflecting the uncertainty and low quality of the evidence.
Trade-off between net clinical effects and costs	No relevant economic studies were identified for this population. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee (see appendix Q). The committee noted the lack of good quality evidence to support the effectiveness of prophylaxis in this population. The committee also noted that currently the risk of VTE is lower given the use of newer types of catheters and the

	fact that most of these people will be ambulant.
Other considerations	The committee noted the use of heparin-coated or heparin-impregnated catheters to prevent catheter-related thrombi. The committee highlighted that rather than a form of VTE prophylaxis for the patient, it has the specific aim of preventing blood clots in the catheter, and therefore was not an intervention explored in this review.
	The committee made a research recommendation on different pharmacological prophylaxis strategies in this population group.

19 People who are having palliative care

19.1 Introduction

The need for provision of palliative care has been recognised across all incurable malignant and non-malignant disease services. In addition, advances in therapeutic interventions have resulted in the palliative care population living longer despite incurable disease.

For the purposes of this guideline a distinction needs to be made between a terminal patient; that is when a patient appears to be approaching death or has been admitted for end of life care, and a palliative patient; which encompasses any patient with incurable disease at any point of their disease journey. This is of particular relevance as it becomes more commonplace for patients with metastatic disease to receive ongoing palliative chemotherapy and targeted anticancer treatments. Palliative care patients may therefore encompass a spectrum of patients all with incurable illness, yet with a breadth of performance status, symptomatology and life expectancy.

19.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are having palliative care?

For full details see review protocol in appendix C.

Table 116: PICO characteristics of review question

Population	Adults and young people (16 years and older) admitted to hospital 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.

Intervention(s)	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 (no minimum duration):
	• Unfractionated heparin (UFH) (low dose, administered subcutaneously)
	• Low molecular weight heparin (LMWH), licensed in UK:
	  o enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)
	  o 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*)
	  o 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)*
Comparison(s)	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: 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.

19.3   Clinical evidence

No relevant clinical studies comparing the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people who are having palliative care. See the study selection flow chart in appendix E and excluded studies list in appendix N.

19.4   Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

19.5   Evidence statements

Clinical

No relevant clinical studies were identified.

Economic
No relevant economic evaluations were identified.

19.6   Recommendations and link to evidence

Recommendations	**1.4.13 Consider pharmacological VTE prophylaxis for people who are having palliative care. Take into account temporary increases in thrombotic risk factors, risk of bleeding, likely life expectancy and the views of the person and their family members or carers (as appropriate):** • **Use LMWH[yyy] as first-line treatment.** • **If LMWH[zzz] is contraindicated use fondaparinux sodium[aaaa]. [2018]** **1.4.14 Do not offer VTE prophylaxis to people in the last days of life.**

[yyy] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the Geeral Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[zzz] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[aaaa] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	[2018] **1.4.15 For recommendations on shared-decision making in the last days of life, see the NICE guideline on care of dying adults in the last days of life. [2018]** **1.4.16 Review VTE prophylaxis daily for people who are having palliative care, taking into account the views of the person, their family members or carers (as appropriate) and the multidisciplinary team. [2018]**
Research recommendation	**None**
Relative values of different outcomes	The committee considered health-related quality of life (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge), pulmonary embolism (up to 90 days from hospital discharge), major bleeding (up to 45 days from hospital discharge) as critical outcomes. The committee considered all-cause mortality (up to 90 days from hospital discharge), fatal PE (up to 90 days from hospital discharge), clinically relevant non-major bleeding (up to 45 days from hospital discharge), heparin-induced thrombocytopenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail explaining prioritisation of the critical outcomes.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	Whilst the true prevalence of VTE in the palliative care population is not known, rates of up to 50% have been reported. However, an audit of 1164 hospice case notes suggested that whilst the majority of patients were at risk of VTE, only 45% would have been eligible (i.e. had no contraindications or were not already anticoagulated) for pharmacological thromboprophylaxis.[84] The committee considered that for palliative care patients it would be reasonable to extrapolate from the acutely ill medical patient population. If the person was an acutely ill medical patient who was at risk of VTE (based on risk assessment) and it would be appropriate to give thromboprophylaxis then the same applies to a palliative care patient whether they be in a hospice or admitted to hospital. Therefore the committee considered it reasonable to offer the same choice of prophylaxis recommendations in this population as the recommendations from the medical population. There is a distinction between palliative care patients (those approaching the end of life including people who are likely to die within 12 months, people with advanced, progressive, incurable conditions and people with life-threatening acute conditions) and people who are admitted for terminal care (people in the last days or hours of life), as for this second population there is little health economic or patient quality of life benefit in offering prophylaxis. Therefore the committee made a 'do not offer' recommendation. The committee noted that there may be difficulty in identifying when a patient may be moving from one state (approaching the end of life) to the next (in the last days of life) and refer clinicians to related guidance Care of dying adults in the last days of life (NG31).
Trade-off between net clinical effects	No relevant economic studies were identified for this population. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee (see

and costs	appendix Q). The committee acknowledged that the cost effectiveness of pharmacological prophylaxis in palliative care patients is difficult to assess because although these patients might have an increased risk of symptomatic VTE, they might also have increased risk of bleeding. Furthermore, the quality-adjusted life years (QALYs) gained would be very small, if there is any gain, especially for people in the last days of life as there is no survival benefit and there might even be a loss in quality of life due to the added medication burden. Hence, the committee considered that, for people in the last days of life, prophylaxis will not be cost-effective. Furthermore, it was determined that symptoms attributable to VTE at the end of life could be managed symptomatically with end of life medications. For people who are receiving palliative care for symptom management, either at hospital or hospice, the cost effectiveness of prophylaxis will be highly dependent on the balance between the bleeding and VTE risks which can change quickly. Hence, the committee considered it would be important to frequently reassess the VTE and bleeding risks in this population. This was also the recommendation in CG92 and reflects current practice. The committee noted that this may require staff time and it was considered to be justified as it means that people will receive the appropriate care for their clinical condition. It also means that prophylaxis could be stopped if no longer needed; reducing waste, or started if needed; avoiding costs associated with VTE events.
	Given the lack of evidence regarding which prophylaxis options would be suitable for this population, the committee considered that extrapolation from the acutely ill medical population would be appropriate.
Other considerations	The committee noted that the palliative care population is very heterogeneous in terms of thrombogenicity, disease stage, performance status and life expectancy. People with advanced incurable disease may live for several years and a terminal diagnosis should not exclude people from consideration of thromboprophylaxis. The committee recognised therefore the difference between palliative care (the management of patients with incurable or life limiting illness) and end of life care (the management of patients in the last days/hours of life). One qualitative study[138] suggested people in a specialist palliative care unit found LMWH acceptable and wished to be involved in discussions about thromboprophylaxis.
	Please also see the relevant nice guidelines on Patient experience in adult NHS services (GC138) and Care of dying adults in the last days of life (NG31).

20 People admitted to critical care units

20.1 Introduction

Patients admitted to a critical care facility (who are generally in need of level 2 or level 3 care) can be separated into some distinct groups by their disease process:

- patients with any acute illness that has resulted in one or more organ systems failing and have a need for interventions to support organ function
- patients who need a higher level of observation and intervention that cannot safely be provided elsewhere
- patients who have had complex or prolonged surgical procedures and hence require a duration of recovery with a higher level of observation and monitoring than can be provided elsewhere in order to rapidly detect and mange any deterioration
- patients who are dying and there is ongoing consideration of organ donation.

Each group has its own unique risk factors for VTE and risks of bleeding or other complications. The unifying feature is that during times of severe physiological upset, the inflammatory response is at a maximum and the patient is almost always immobile and likely to have a number of intravascular catheter devices. This puts the patient at a much higher risk of developing venous thrombi. The same patient may however also be at an increased risk of bleeding, either due to a coagulopathy as a consequence of their disease or interventions; or be at risk of bleeding into a surgical field with disastrous consequences such as in spinal surgery or neurosurgery. The medications and equipment used in critical care may increase the risk of bleeding further.

Critically ill patients will have a number of such risk factors which may change in nature, number and significance many times throughout their stay. Also, many invasive procedures may be carried out during such an admission (central lines, lumbar punctures, chest drains etc) and so relative risks of bleeding as a consequence will also change many times.

20.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people admitted to critical care units?

For full details see review protocol in appendix C.

Table 117: PICO characteristics of review question

Population	Adults and young people (16 years and older) admitted to critical 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 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 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.

20.3 Clinical evidence

One study which compared the effectiveness of different prophylaxis treatments for people admitted to critical care units was included in the previous guideline (CG92) [54]. However, this study was excluded from the update because the inclusion criteria reported in the study was not appropriate for this review. Patients included in this study previously had a DVT event or presence of signs of a DVT at inclusion.

A search was conducted for randomised trials comparing the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people admitted to the critical care units. Two randomised controlled trials were included [39] [192] these are summarised in Table 118 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 119 and Table 120). See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

Table 118: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes
Cook 2011 [39]	Intervention (n=1873): LMWH, dalteparin, 5000IU once daily (standard dose), subcutaneously administered. Research pharmacists prepared identical syringes for subcutaneous injection of either dalteparin once daily plus placebo once daily (details about the placebo used is not reported). Participants received prophylaxis for	n= 3746 People who remained in ICU for at least 3 days Diagnosis on admission: Cardiovascular condition – 9.0% Respiratory condition – 45.6% Gastrointestinal condition – 14.0% Renal condition – 1.74%	Mortality in ICU and hospital (up to 100 days) DVT (at time of death, discharge or at 100 days if patients were still hospitalised): 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.

Study	Intervention and comparison	Population	Outcomes
	duration of stay in ICU. Comparison (n=1873): UFH, 5000IU twice daily, subcutaneously administered. Participants received prophylaxis for duration of stay in ICU.	Neurologic condition – 6.14% Sepsis – 14.73% Metabolic condition – 3.87% Other medical condition – 1.74% Other surgical condition – 3.16% Age (range): 44.6-78.1 Gender (male to female ratio): 1.32:1 Canada, Australia, Brazil, Saudi Arabia, USA and the UK	PE (at time of death, discharge or at 100 days if patients were still hospitalised): defined as characteristic intraluminal filling defect on computed tomography of the chest, a high probability ventilation-perfusion scan, or autopsy finding. Major bleeding (at time of death. discharge or at 100 days if patients were still hospitalised): 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. Heparin induced-thrombocytopenia (at time of death. discharge or at 100 days if patients were still hospitalised)
Vignon 2013 [192]	Intervention (n=205): Intermittent pneumatic compression (IPCD) devices and AES. IPC was achieved with using a compression system with adapted tubing sets and thigh (half-leg) sleeves. AES consisted of thigh-length AES. Participants received prophylaxis for 6 days. Comparison (n=202): AES only, thigh-length AES. Participants received prophylaxis for 6 days.	n= 407 People admitted to ICU with a high risk of bleeding Contraindicated to pharmacological prophylaxis Primary admission diagnostic category (%): Spontaneous intracranial haemorrhage - 36% Traumatic intracranial haemorrhage - 21.4% Multisystem trauma - 10.8% Other haemorrhage - 9.9%	DVT (symptomatic and asymptomatic): assessed using compression ultrasonography PE, symptomatic (6 days): no definition reported Fatal PE (6 days): no definition reported

Study	Intervention and comparison	Population	Outcomes
		Severe sepsis or septic shock - 9.6% Acute respiratory distress syndrome - 5.9% Other diagnoses - 6.4% Age (mean): 55.4 years Gender (male to female ratio): 1.96:1 France	

20.3.1 LMWH (standard dose; standard duration) versus UFH in people admitted to ICUs

Table 119: Clinical evidence summary: LMWH (standard dose; standard duration) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH	Risk difference with LMWH (95% CI)
All-cause mortality	3746 (1 study) up to 100 days	MODERATE[b] due to indirectness	RR 0.91 (0.84 to 0.99)	407 per 1000	37 fewer per 1000 (from 4 fewer to 65 fewer)
DVT (symptomatic and asymptomatic)	3746 (1 study) at time of death, discharge or at 100 days if patients were still hospitalised	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.86 (0.69 to 1.07)	86 per 1000	12 fewer per 1000 (from 27 fewer to 6 more)
PE	3746 (1 study) at time of death, discharge or at 100 days if patients were still hospitalised	LOW[b,c] due to indirectness, imprecision	RR 0.64 (0.36 to 1.16)	15 per 1000	5 fewer per 1000 (from 10 fewer to 2 more)
Major bleeding	3746 (1 study) at time of death, discharge or at 100 days if patients were still hospitalised	LOW[b,c] due to indirectness, imprecision	RR 0.98 (0.75 to 1.28)	56 per 1000	1 fewer per 1000 (from 14 fewer to 16 more)
Heparin-induced thrombocytopenia	3746 (1 study) at time of death, discharge or at 100 days if patients were still hospitalised	LOW[b,c] due to indirectness, imprecision	RR 0.42 (0.15 to 1.18)	6 per 1000	4 fewer per 1000 (from 5 fewer to 1 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

20.3.2 People who are contraindicated to pharmacological prophylaxis

Table 120: Clinical evidence summary: IPCD (half-leg) and AES versus AES

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES only	Risk difference with IPCD + AES (95% CI)
DVT (symptomatic and asymptomatic)	362 (1 study) 6 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.64 (0.3 to 1.37)	87 per 1000	31 fewer per 1000 (from 61 fewer to 32 more)
PE	406 (1 study) 6 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.13 (0 to 6.75)	5 per 1000	4 fewer per 1000 (from 5 fewer to 28 more)
Fatal PE	406 (1 study) 6 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	[d]	[d]	0 fewer per 1000 (from 10 fewer to 10 more)[d]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

d Zero events in both arms. Risk difference calculated in Review Manager.

20.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

20.5 Evidence statements

Clinical

LMWH at a standard dose for a standard duration was compared with UFH, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and heparin-induced thrombocytopenia were reported in one study. There was clinical benefit of LMWH in terms of all-cause mortality, possible clinical benefit of LMWH in terms of PE and heparin-induced thrombocytopenia, although all these findings could also be consistent with no difference. There was no clinical difference in terms of DVT (symptomatic and asymptomatic) and major bleeding, however there was some uncertainty around these results. The quality of the evidence ranged from very low to moderate due to risk of bias, indirectness and imprecision.

People who are contraindicated to pharmacological prophylaxis

IPCD (half-leg) in combination with AES was compared with AES, the outcomes DVT (symptomatic and asymptomatic), PE and fatal PE were reported in one study. There was possible clinical benefit of IPCD in combination with AES in terms of DVT (symptomatic and asymptomatic) and PE. However the uncertainty around these results means they are also consistent with no difference or clinical harm. There was no clinical difference in terms of fatal PE. The quality of the evidence was very low due to risk of bias, indirectness and imprecision.

Economic

- No relevant economic evaluations were identified.

20.6 Recommendations and link to evidence

Recommendations	**1.4.17 Assess all people admitted to the critical care unit for risk of VTE and bleeding. [2018]**
	1.4.18 Provide LMWH[bbbb] to people admitted to the critical care unit if pharmacological VTE prophylaxis is not contraindicated. For people with renal impairment see recommendations 1.4.7 and 1.4.8. [2018]
	1.4.19 Consider mechanical VTE prophylaxis for people admitted to the critical care unit if pharmacological prophylaxis is contraindicated based on their condition or procedure. [2018]

[bbbb] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	1.4.20 If using mechanical VTE prophylaxis for people admitted to the critical care unit, start it on admission and continue until the person no longer has reduced mobility relative to their normal or anticipated mobility. [2018] **1.4.21 Reassess VTE and bleeding risk daily for people in critical care units. [2018]** **1.4.22 Assess VTE and bleeding risk more than once a day in people admitted to the critical care unit if the person's condition is changing rapidly. [2018]**
Research recommendation	**None**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days after leaving ICU), deep vein thrombosis (symptomatic and asymptomatic) (7–90 days after leaving ICU), pulmonary embolism (7–90 days after leaving ICU), major bleeding (up to 45 days after leaving ICU) and fatal PE (7–90 days after leaving ICU) as critical outcomes. The committee considered clinically relevant non-major bleeding (up to 45 days after leaving ICU), health-related quality of life (up to 90 days after leaving ICU), heparin-induced thrombocytopenia (duration of study), technical complications of mechanical interventions (duration of study) and line associated thrombosis (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	Two randomised controlled trials were included in this review. One of these studies evaluated the use of LMWH (dalteparin) versus unfractionated heparin (UFH) for people admitted to critical care units. The quality of the evidence ranged from very low to moderate. Evidence was downgraded due to risk of bias, indirectness and imprecision. Outcomes were downgraded for indirectness due to an inappropriate time point, past the time-point set by the committee (up to 90 days after leaving ICU). The other included study evaluated the use of IPCD with AES versus AES alone. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.
Trade-off between clinical benefits and harms	This is a critically ill population where survival is the most immediate concern. Patients may be admitted into critical care from different wards within the hospital, representing a worsening of the person's condition. Therefore it is important to reassess the person's risk on admission to ICU as risk may differ from first assessment and the clinical condition may have changed. Critical care is a recognised risk factor for increasing VTE risk (it is a factor in both the Department of Health risk assessment list and risk tools such as the 7-factor version of IMPROVE) and as such the committee considered that in absence of bleeding risk factors and after taking into account planned interventions or therapies which may increase complications, VTE prophylaxis should be offered. Moderate quality evidence showed a clinically important difference in mortality rate in those offered LMWH compared to those offered UFH. No evidence was identified for any other pharmacological intervention. Therefore the committee felt comfortable recommending LMWH for this population. The committee noted that renal impairment is a concern within this population and advise clinicians to refer to the renal impairment recommendation when applicable. Due to the high VTE risk in this population, if people were contraindicated for

	pharmacological prophylaxis, the committee recommended considering mechanical prophylaxis.
	As the clinical situation changes it is necessary to reassess the risks of VTE and bleeding. For this reason the committee did not state a recommended duration for LMWH as they considered it would be up to clinical judgement based on the daily reassessment of changing VTE and bleeding risk.
Trade-off between net clinical effects and costs	No economic studies were included for this population. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee (see appendix Q). The committee acknowledged that there will be a cost impact given the need for more staff time to complete the assessment on admission to the critical care unit, but this will be off-set by the potential benefits for reducing the risk of having a costly VTE event. The committee noted that the clinical evidence showed a clinical benefit for LMWH versus UFH in terms of PE, heparin-induced thrombocytopenia and mortality and considered that the higher cost of using LMWH would be offset by the downstream cost saving from averted PEs and HIT.
	For people in whom pharmacological options are contraindicated, the committee considered that the evidence available supported the use of mechanical prophylaxis given the high risk of VTE in this population.
Other considerations	Patients treated in the critical care unit may be unconscious or not capable of making decisions about their treatment. In such situations, decisions about care should take into account the known view of patients and discussions with family members, where appropriate.

21 Pregnant women and women up to 6 weeks post-pregnancy

21.1 Introduction

Pregnancy is a highly prothrombotic state and temporary illness and/or immobilisation will lead to a further increased risk of VTE. The increased risk of VTE is present from early pregnancy and does not revert completely to normal until at least 6 weeks after delivery, especially after an emergency caesarean section. The time of greatest risk for VTE associated with pregnancy is the early postpartum period and, although in absolute terms most VTE events occur antenatally, the risk per day is greatest in the weeks immediately after delivery.

The scope for this current guideline relates to people admitted to hospital or attending hospital for day procedures. This section reviews the evidence for prophylaxis for women who are pregnant and up to 6 weeks post-pregnancy who are admitted to hospital or are attending hospital for day procedures. This includes to give birth, complications related to the pregnancy and to manage conditions other than their pregnancy, for example management of pre-existing disease such as diabetes, or acute surgery.

21.2 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)?

For full details see review protocol in appendix C.

Table 121: PICO characteristics of review question

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 of pregnancy)

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)
	   o 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:
	   o Enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)
	   o 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*)
	
	   o 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:
	
	   o Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)
	
	   o Certoparin (3000 units daily)
	
	   o Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)
	
	   o Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)
	
	   o 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 • 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) (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.

21.3   Clinical evidence

Three studies were included in the review;[23, 41, 76] these are summarised in **Table 122** below. One of these was included in the previous guideline (CG92)[57] and has now been excluded. One study that was excluded from the previous guideline has now been included [23]. Two further studies were identified for inclusion[41, 76]. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 123, Table 124, Table 125, Table 126 and Table 127). See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

All of the evidence identified is from a population of women undergoing a caesarean section. One study[174] was identified in a predominately vaginal birth population, but did not report on any protocol outcomes except for symptomatic DVT only, and therefore was not analysed. Details of the paper can be found in appendix H.

Table 122: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Burrows 2001[23]	Intervention (n=39): LMWH, low dose (dalteparin, 2500U, once daily) Administered 4-24 hours postoperatively and continued for 5 days Comparison (n=37): No VTE prophylaxis (placebo, saline)	n=76 People who had elective or emergency caesarean section (Elective 60.5%, emergency 39.5%) Age, years (mean, SD): intervention (31.7, 4.8), comparison (31.3, 5.5) Australia	PE (42 days): confirmed by pulmonary angiography, ventilation lung scanning or venography Major bleeding (42 days): defined as >20g/L fall in haemoglobin, the need for a blood transfusion of >2 units of blood, retroperitoneal, intraocular or intracranial bleeds)	
Cruz 2011[41]	Intervention (n=311): LMWH, high dose (bemiparin, 3500U, once daily). Administered at least 8 hours following	n=646 Patients with a caesarean birth Age, years (mean, SD):	PE (90 days): confirmed by perfusion lung scintigraphy and Doppler ultrasound	

Study	Intervention and comparison	Population	Outcomes	Comments
	caesarean for 5 days Comparison (n=335): LMWH, high dose (bemiparin, 3500U, once daily). Administered at least 8 hours following caesarean for 10 days	intervention (31.37, 5.24), comparison (31.06, 5.62) Spain		
Heilmann 2007[76]	Intervention 1 (n=50): LMWH, standard dose (dalteparin, 5000U, once daily). Administered 6 hours following caesarean, for 7 days Intervention 2 (n=50): UFH (5000U). Unclear if UFH was given two or three times daily. Administered 6 hours following caesarean, for 7 days Comparison (n=50): AES, length not reported. Administered 6 hours following caesarean, for 7 days	n=150 Patients with uncomplicated pregnancy undergoing caesarean section Age, years (mean, SD): LMWH group (28, 6), UFH group (29, 5), control group (28, 3) BMI >26 (kg/m^2) = 1.3% Germany	DVT (symptomatic and asymptomatic) (up to hospital discharge): screened by Impedance plethysmography or Doppler ultrasound	Stratified by risk then randomised. Low risk control group. Higher risk randomised to one of the heparin groups.

Table 123: Clinical evidence summary: UFH versus AES (length unspecified)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with UFH (95% CI)
DVT (symptomatic and asymptomatic)	100 (1 study) discharge from hospital	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1 (0.06 to 15.55)	20 per 1000	0 fewer per 1000 (from 19 fewer to 291 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 124: Clinical evidence summary: UFH versus LMWH (standard dose, standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH	Risk difference with UFH (95% CI)
DVT (symptomatic and asymptomatic)	100 (1 study) discharge from hospital	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 7.39 (0.15 to 372.38)	0 per 1000	-d

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Absolute effects could not be calculated due to zero events in one of the arms.

Table 125: Clinical evidence summary: LMWH (low dose, standard duration) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (low dose) (95% CI)
PE	76 (1 study) 42 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c,d]	0 fewer per 1000 (from 50 fewer to 50 more)[c,d]
Major bleeding	76 (1 study) 42 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0 to 6.47)	27 per 1000	23 fewer per 1000 (from 27 fewer to 125 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Could not be calculated as there were no events in the intervention or comparison group
d Risk difference calculated in Review Manager

Table 126: Clinical evidence summary: LMWH (standard dose, standard duration) versus AES (length unspecified)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with LMWH (95% CI)
DVT (symptomatic and asymptomatic)	100 (1 study) discharge from hospital	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.14 (0 to 6.82)	20 per 1000	17 fewer per 1000 (from 20 fewer to 102 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 127: Clinical evidence summary: LMWH (high dose, extended duration) versus LMWH (high dose, standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (standard duration)	Risk difference with LMWH (extended duration) (95% CI)
PE	646 (1 study) 90 days	VERY LOW[a,c] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 10 fewer to 10 more)[e]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d Could not be calculated as there were no events in the intervention or comparison group

e Risk difference calculated in Review Manager

21.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

21.5 Evidence statements

Clinical

Very low quality evidence from one study (n=100) showed no difference for DVT between unfractionated heparin and anti-embolism stockings, and a possible benefit when using LMWH (standard dose, standard duration) compared to either anti-embolism stockings or UFH but there was very high uncertainty around these results.

When comparing LMWH (low dose, standard duration) against no prophylaxis, very low quality evidence from one study (n=76) showed no difference with respect to PE and a possible benefit of LMWH for DVT but there was very high uncertainty around this effect estimate.

Very low quality evidence from one study (n-646) found no difference between PE rates when comparing LMWH (high dose, standard duration) with LMWH (high dose, extended duration).

Economic

No relevant economic evaluations were identified.

21.6 Recommendations and link to evidence[cccc]

Recommendations	**1.6.1 Consider LMWH[dddd] for all women who are admitted to hospital or a midwife-led unit if they are pregnant or gave birth, had a miscarriage or had a termination of pregnancy in the past 6 weeks, and whose risk of VTE outweighs their risk of bleeding. [2018]**
	1.6.2 Do not offer VTE prophylaxis to women admitted to hospital or a midwife-led unit who are in active labour. [2018]
	1.6.3 Stop pharmacological VTE prophylaxis when women are in labour. [2018]
	1.6.4 If using LMWH[eeee] in pregnant women, start it as soon as possible and within 14 hours of the risk assessment being completed and

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[cccc] Recommendations for this section appear in a different order to the summary list in section 1.1.

[dddd] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[eeee] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	continue until the woman is no longer at increased risk of VTE or until discharge from hospital or the midwife-led unit. [2018] **1.6.5 If using LMWH**[ffff] **in women who gave birth or had a miscarriage or termination of pregnancy, start 4–8 hours after the event unless contraindicated and continue for a minimum of 7 days. [2018]** **1.6.6 Consider combined prophylaxis with LMWH**[gggg] **plus mechanical prophylaxis for pregnant women or women who gave birth or had a miscarriage or termination of pregnancy in the past 6 weeks and who are likely to be immobilised, or have significantly reduced mobility relative to their normal or anticipated mobility for 3 or more days after surgery, including caesarean section:** • **Use intermittent pneumatic compression as first-line treatment.** • **If intermittent pneumatic compression is contraindicated use antiembolism stockings.** **Continue until the woman no longer has significantly reduced mobility relative to her normal or anticipated mobility or until discharge from hospital. [2018]**
Research recommendation	**4. What is the clinical and cost effectiveness of fixed dose compared to weight-adjusted dose of LMWH for pregnant women admitted to hospital (including up to 6 weeks after giving birth)?**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge pulmonary embolism (symptomatic and asymptomatic) (up to 90 days from hospital discharge), fatal PE (up to 90 days from hospital discharge), and major bleeding (up to 45 days from hospital discharge) as critical outcomes. The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), and technical complications of mechanical interventions (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	Four studies were included in this review with five comparisons. The comparisons evaluated both pharmacological and mechanical interventions. The pharmacological interventions included LMWH and UFH. The only mechanical intervention identified was AES. No evidence was found for other types of pharmacological or mechanical prophylaxis. All of the evidence in the review was judged to be very low quality. The committee noted that across the small amount of evidence for this population, lack of adequate randomisation and allocation concealment was an issue. The committee noted that the evidence for this population came from a small number of underpowered studies. Therefore much of the evidence was further downgraded

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[ffff] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[gggg] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	due to imprecision as the confidence intervals around the effect estimates were very wide.
Trade-off between clinical benefits and harms	The review covered pregnant women following admission at any stage of pregnancy but the included studies only covered a caesarean population, and there was no evidence for antenatal admissions (for example pregnant women coming in to have diabetes controlled or admitted for pre-eclampsia), or post-surgery in early pregnancy (for example termination of pregnancy) or for those undergoing a spontaneous or instrumental/assisted vaginal birth.

Pharmacological prophylaxis

UFH and LMWH do not cross the placenta so are considered safe for the foetus as opposed to warfarin or DOACs. The committee discussed the evidence for UFH, and noted that there was no evidence of a clinical benefit for the outcome reported, DVT. Additionally the subgroup highlighted the risk of osteoporosis with prolonged use of UFH. The subgroup and committee therefore concluded that UFH was not to be recommended due to the need for multiple injections given its short half life, and lack of evidence that it is an effective method of prophylaxis in this population.

Evidence for LMWH was identified at both a standard and extended duration. The subgroup and committee noted that although the evidence was limited, there was some evidence of a possible clinical benefit of LMWH for DVT and major bleeding, however there was very high uncertainty around these results. When considering the duration of LMWH prophylaxis, it was noted that there was no clinical difference between standard and extended duration prophylaxis. The subgroup considered the duration of prophylaxis in surgical populations, and also considered it was important to allow for clinical judgement.

Mechanical prophylaxis

The subgroup discussed the evidence for AES, and noted that there was no evidence of clinical benefit for the DVT outcome, with no other outcomes reported.

When considering women undergoing a caesarean section, the subgroup considered evidence from the surgical populations, particularly those having abdominal surgery. However, it was acknowledged that caesarean sections would take less time than other surgical procedures (anecdotally a caesarean involves anaesthesia for 60 minutes with the actual surgery taking approximately 40 minutes, or longer if there are additional factors such as obesity, previous scar tissue, placenta pravia or haemorrhage), and therefore this population of patients would have less overall immobilisation time (immobile for approximately 4–6 hours and then up and about dealing with the baby). It was also noted that the population of women undergoing caesarean section would generally be of better health compared to most surgical populations.

Combined prophylaxis

No evidence was identified for combined pharmacological and mechanical prophylaxis. However in line with recommendations in the abdominal surgery population, the committee determined that it may be considered on occasions where women are likely to be immobilised, or have significantly reduced mobility relative to their normal or anticipated mobility, for 3 or more days post- surgery. In terms of which mechanical prophylaxis to recommend, the committee acknowledged evidence of harm and evidence of no effect of AES in other populations (such as the CLOTS 1, 2, and 3 trials included in the review for prophylaxis in the acute stroke population) when the ubiquity of AES in many settings has been questioned in the absence of clear evidence of their effectiveness. It was also anecdotally acknowledged that there is generally poor follow-up of harm and usage/adherence with AES. The subgroup and committee discussed a recommendation against the use of AES, but it was considered that there was not enough evidence to support this. The committee considered that evidence from other populations for the effectiveness of IPC was stronger and therefore IPC was the preferred choice of mechanical prophylaxis when additional prophylaxis was

	deemed necessary. The committee highlighted that IPC can only be used when in bed or sitting down, which reinforced that this should only be considered for people who would be immobilised, or have significantly reduced mobility relative to their normal or anticipated mobility, for 3 or more days post-surgery. Postpartum women are usually able to mobilise to get themselves to the bathroom within a day.
	The subgroup discussed the population of women not undergoing a surgical procedure, and noted that unlike the surgery population, women not having a caesarean section are generally healthy, and there is no increased risk of bleeding. Therefore mechanical prophylaxis would not be necessary or beneficial.
	Prophylaxis when women are in labour
	The subgroup discussed the need for interruption of thromboprophylaxis for women who go into active labour or who are admitted in active labour. Although there is no evidence on which to base the decision, there is clear guidance on the interval required between thromboprophylaxis administration and neuroaxial anaesthesia/analgesia and to allow for the possibility of those who may require emergency caesarean section. Interruption of thromboprophylaxis increases the likelihood of being able to administer neuroaxial anaesthesia/analgesia and thus may avoid complications associated with a general anaesthetic. Additionally, if bleeding does occur then no additional harm is caused by the administration of LMWH and the risk of bleeding can be minimised.
Trade-off between net clinical effects and costs	No economic studies were identified for this population. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee (see appendix Q). The committee considered the clinical evidence which showed a possible benefit for LMWH as a pharmacological prophylaxis in those assessed to be at high risk of VTE and low risk of bleeding. This was considered to be in line with current practice. However, the committee also noted that the practice of prescribing LMWH in weight-adjusted doses is not evidence-based. Based on these suggested doses, the daily cost of LMWH would range from £4 to £6 for a pre-pregnancy body weight of 91 to 130 kg and from £6 to £7 for a body weight of 131 to 170 kg. This is compared to a daily cost of £3 to £4 for a normal body weight of 50 to 90 kg. Given the large volume of caesarean operations, this practice would have a considerable cost impact with no evidence to suggest that weight-adjusted dosing is clinically effective and, hence, is unlikely to be cost effective.
	The committee also noted the lack of evidence to support a recommendation of a specific duration of prophylaxis with LMWH. It was acknowledged that this will require clinical judgement and individual assessment. Longer duration of prophylaxis will be more costly but might be considered essential for the avoidance of VTE events if the VTE risk factors, such as the length of immobilisation, are likely to continue for a long duration. The clinical evidence did not show a benefit for UFH, hence the committee did not consider this option would be a cost-effective prophylaxis strategy to recommend.
	When discussing the mechanical prophylaxis options, the committee considered the cost of AES which ranges from £4 to £9 per pair on average, and the cost of nurse time required for monitoring and fitting to ensure adherence with their recommended use. The committee considered that in absence of a clear evidence of benefit to justify this large cost, the use of AES is not likely to represent a cost-effective prophylaxis option. The committee considered that in women who have a contraindication to using pharmacological prophylaxis, the preferred mechanical prophylaxis option would be IPCD. This was based on extrapolation of evidence from other populations, such as stroke patients. The committee also reported that IPCDs are usually available to hospitals on a rent-free basis and the only cost involved is that of the sleeves (£21–£32 per pair). The committee considered this is likely to be offset by the savings from the reduced use of AES in this and other populations.
Other considerations	The committee wished to highlight that while evidence for the post-caesarean population was sometimes extrapolated from other post-surgical populations,

pregnant women are generally healthy and undergoing a physiological event in comparison to the older, more medically ill surgery population. Women who have had a caesarean section are mobilised much sooner (same day/next day) compared to the time periods covered in some of the studies. However the subgroup also noted that women have a higher average BMI now than the populations featured in the earlier studies.

With advice from the obstetric subgroup, the committee discussed weight-adjusted dosing of LMWH for thromboprophylaxis in pregnant women. They acknowledged that the BNF and RCOG guidelines[168] both consider weight-adjusted dosing, however the latter state there is no evidence to guide appropriate weight-adjusted doses. The committee recognised that weight-adjusted doses are used but considered that there is inadequate evidence to recommend this for pregnant women. One available RCT on differing doses of post-caesarean enoxaparin in obese women was excluded from the review as the primary outcomes did not match the review protocol (proportion of patients with peak anti-Xa levels in the prophylactic range of 0.2 to 0.6 IU ml^{-1} rather than hard outcomes of reduction in DVT/PE) however they identified no cases of VTE in either the weight-adjusted intervention group or the fixed dose comparison group (major bleeding was not identified as an outcome). [180] Increasing dose by weight would have significant cost implications and the subgroup agreed that they were not in a position to recommend weight-adjusted dosing with the absence of evidence to back up this change.

Duration of LMWH

The guideline committee acknowledged that there is limited evidence for the most effective duration of LMWH for VTE prophylaxis. The duration of 7 days was recommended as it is the average duration presented in the trials evaluated throughout the guideline. It was also noted that studies such as the Million Women Study[116] have shown that the risk of VTE extends post-discharge, shorter doses of LMWH are less likely to reduce risk of VTE.

Timing of prophylaxis

Current practice reflects that most wards give their LMWH once a day at 6pm, however for people who may miss this round the committee wanted to ensure that the first dose could be given in a timely fashion. The committee recommend a time point that is in line with current NHS policy on time to consultant review of acute inpatients. This standard states that all emergency admissions must be seen and have a thorough clinical assessment by a suitable consultant as soon as possible but at the latest within 14 hours from the time of admission to hospital.[134] The committee agreed that recommending a similar timeframe within which pharmacological prophylaxis should be given (if indicated by risk assessment) makes logical clinical sense and will ensure clinical care is not delayed. However in the postpartum context, the administration of LMWH should be delayed for 4 hours postpartum as this is the most high-risk time for primary postpartum haemorrhage to occur and for surgical intervention to be required to arrest bleeding or repair any obstetric injuries. The 4–8 hour timeframe allows time to check post-delivery outcome. The committee noted that there is no evidence to support this time-frame but considered expert opinion, comments on current practice and feasibility.

Setting

Pregnant women and women who gave birth or had a miscarriage or termination of pregnancy in the past 6 weeks may be seen in hospital or in a midwife-led unit. The exception is women who are likely to be immobilised for 3 or more days after surgery (including caesarean section). It would be unusual for these women to be in a midwife-led unit rather than hospital. There may be rare occasions where a woman has had a baby and surgery and been immobile for three or more days and is then transferred to a midwife-led unit during recovery. For example if maternity wards are particularly busy women may request transfer to a midwife-led unit before they are fully fit and mobile. However, the committee recognised that this was a rare situation and that the recommendations covering immobility would be best related

to the hospital setting only. The committee made a research recommendation on weight-based dose-adjustment strategies in this population group.

Regional anaesthesia - epidural or spinal catheter

A significant number of women giving birth will have regional anaesthesia peri-delivery. The obstetric subgroup noted that most clinicians avoid VTE prophylaxis in the form of LMWH for at least 4 hours or longer after insertion of an epidural or spinal catheter. An epidural should not be inserted or removed for at least 12 hours after a prophylactic dose of LMWH. These timings all vary from unit to unit, there is an absence of evidence in regards to the most effective time for removal and insertion of catheters.

22 People with psychiatric disorders

22.1 Introduction

People with psychiatric disorders may be at risk of developing venous thromboembolism, particularly when acutely unwell and admitted to hospital. This may be due to the presence of risk factors such as reduced mobility due to psychiatric illness or sedation, dehydration due to poor oral intake, or comorbid physical illness. The use of antipsychotic medication also increases thrombotic risk. Parity of esteem for mental health is a priority for healthcare, and should include equity of provision for the management of physical health problems in those people presenting primarily with mental illness.

Although previous guidance was applicable to people admitted to psychiatric units, current practice is variable and there is no clearly identifiable national standard. As such there is likely to be variation in assessment and treatment of this population. There are issues which may cause concern with regard to VTE prophylaxis in this population, such as capacity to consent to interventions, interactions of psychotropic medications with pharmacological thromboprophylaxis, and risk issues around the use of pharmacological and mechanical prophylaxis strategies for people who self-harm.

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

For full details see review protocol in appendix C.

Table 128: PICO characteristics of review question

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

Intervention(s)	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 (2.5mg twice daily) • Dabigatran (220mg once daily; 150mg once daily - patients with moderate renal impairment, interacting medicines, over 75 years old) • Rivaroxaban (10mg once daily) • Aspirin (up to 300mg)* *off-label
Comparison(s)	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 • Pre-operative 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)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.

22.3 Clinical evidence

No relevant clinical studies comparing the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people with psychiatric disorders. See the study selection flow chart in appendix E and excluded studies list in appendix N.

22.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

22.5 Evidence statements

Clinical

No relevant clinical studies identified.

Economic

No relevant economic evaluations were identified.

22.6 Recommendations and link to evidence

Recommendations	**1.4.23 Assess all acute psychiatric patients to identify their risk of VTE and bleeding:** • **as soon as possible after admission to hospital or by the time of the first consultant review** • **using a tool published by a national UK body, professional network or peer-reviewed journal. The most commonly used risk assessment tool for hospital patients is the Department of Health VTE risk assessment tool**[hhhh] **(See Appendix T). [2018]** **1.4.24 Reassess all people admitted to an acute psychiatric ward for risk of VTE and bleeding at the point of consultant review or if their clinical**

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	condition changes. [2018] **1.4.25 Consider pharmacological VTE prophylaxis with LMWH[iiii] for people admitted to an acute psychiatric ward whose risk of VTE outweighs their risk of bleeding. [2018]** **1.4.26 Consider pharmacological VTE prophylaxis with fondaparinux sodium[jjjj] if LMWH[kkkk] is contraindicated for people admitted to an acute psychiatric ward whose risk of VTE outweighs their risk of bleeding. [2018]** **1.4.27 Continue pharmacological VTE prophylaxis for people admitted to an acute psychiatric ward until the person is no longer at increased risk of VTE. [2018]**
Research recommendation	**5. What is the burden of VTE associated disease and risk factors (including antipsychotic drugs) in psychiatric inpatients?**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (up 7–90 days from hospital discharge), pulmonary embolism (up to 7–90 days from hospital discharge), fatal PE (7–90 days from hospital discharge), and major bleeding (up to 45 days from hospital discharge) as critical outcomes. The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), heparin-induced thrombocytopenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail explaining prioritisation of the critical outcomes.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	The committee noted that there were no randomised controlled trials evaluating the use of pharmacological and/or mechanical prophylaxis in inpatients with psychiatric disorders. However, the committee were aware that there is evidence from observational studies in this area,[11, 38] which were not included in this evidence review as defined in the protocol. Due to the lack of evidence available the committee made consensus recommendations for VTE risk assessment and prophylaxis for patients admitted to an acute psychiatric ward in line with the recommendations for the population of acutely ill medical patients admitted to hospital. Based on expert psychiatric opinion it was considered that patients who are admitted to an acute psychiatric ward in the UK as these patients are similar to the

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iiii At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

jjjj At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

kkkk At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

medically ill inpatient population in that they are acutely ill individuals who require hospitalisation. However, the committee recognised that there are particular issues for the psychiatric population that differ from general medical patients. One concern is the potential for drug interactions (antipsychotics with chemical prophylaxis); including around co-administration of selective serotonin reuptake inhibitors (SSRIs) which may be associated with an increased bleeding risk although there is no clear evidence on the quantification of this risk.

There are also practical issues of administering mechanical and chemical prophylaxis for psychiatric patients, such as the potential ligature risk when administering AES and concern about administering anticoagulants to people who may self-harm, particularly through cutting. Due to these concerns the committee discussed the importance of teaching and training requirements for healthcare staff (particularly psychiatric nursing staff) with respect to carrying out risk assessment for VTE and administering both mechanical and pharmacological prophylaxis to patients on an acute psychiatric ward. The committee considered that this would improve following the addition of the population-specific prophylaxis recommendation in the current update. Another practical issue is training about how to stock and store prophylaxis drugs. There are also particular concerns around patients' decision-making capacity with respect to consenting to subcutaneous injections and the subsequent teaching/training of mental health professionals. This will have an ongoing effect on reassessment of these patients as their capacity levels fluctuate. People who become acutely mentally ill and require urgent or emergency admission to mental health units may be at particularly high risk of VTE due to dehydration secondary to poor oral intake and/or excessive activity. They may also have relative immobility due to reduced levels of activity which forms part of their psychiatric illness, or due to sedation post tranquillisation with psychotropic medication. In addition people in this situation may have difficulties engaging with assessment processes and in decision making with regards to their care. Consequently, the committee noted that as with other populations, prophylaxis decisions for psychiatric inpatients should be clearly documented and they should be reassessed throughout their stay as it likely that their clinical condition could change unexpectedly.

The committee did not believe there was the evidence to extend the recommendations to psychiatric patients not admitted to an acute psychiatric ward and therefore made no statement about prophylaxis in this group.

Trade-off between net clinical effects and costs	No relevant economic studies were identified for this review. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee (see appendix Q). The committee noted that although CG92 did not explicitly mention people admitted to an acute psychiatric ward, this group was considered to be similar to the acutely ill medical inpatients in relation to their physical health and VTE prophylaxis needs and should have been treated similarly. This has been acknowledged by some trusts where current practice is in line with the recommendation for acutely ill medical inpatients from CG92. However, there is large variation in practice across England and standardisation is required. Hence, a specific recommendation for this population was seen as essential.
	The committee was advised that risk assessment should identify people with increased risk of VTE who would require prophylaxis. This will ensure that prophylaxis is offered only to those who would benefit from it; hence maximising its value and ensuring that the cost of providing prophylaxis is offset by the benefit from reduced VTE events.
	Due to the lack of clinical evidence directly relevant to this population, the committee considered that the prophylaxis options recommended for people admitted for an acute medical illness would be the most relevant evidence that would apply to this population. This agrees with the approach taken in CG92.
	The committee acknowledged that an explicit recommendation for this population may have resource impact in the short term, as more mental health trusts start to routinely undertake risk assessment and prophylaxis provision. However they

	highlighted that this is unlikely to be substantial, given the targeted nature of prophylaxis provision to those subgroups that are assessed to be at increased risk of VTE (for example those temporarily admitted under Section 136 and those receiving antipsychotics).
Other considerations	The population of people with psychiatric conditions was not previously considered in CG92. A review on VTE prophylaxis in psychiatric patients was included in the guideline update due to a MHRA report[114] published in 2009 which reviewed the association between antipsychotic drugs and the risk of VTE. This concluded that an increased risk of VTE cannot be excluded in psychiatric patients.
	The committee noted that local trusts have acknowledged the need for VTE risk assessment in the psychiatric inpatient population and have different local protocols. For example, within the Oxford Health NHS Foundation Trust, the NHS Safety Thermometer was introduced. This is a local improvement tool that is used within hospital settings in various wards (including psychiatric units). It measures the proportion of patients that are 'harm-free' which includes VTE prophylaxis as a category. In 2012 a re-audit was performed that assessed documentation and management of VTE risk in adults admitted to psychiatric units which found that there were general improvements in the documentation of the VTE risk assessment in psychiatric units. However, the committee noted that there is a need for national standard practices/recommendations to ensure equality across trusts.
	Additionally the committee considered it was necessary to present a research recommendation to investigate and quantify the basis and extent of the risk of VTE in the psychiatric population, as there is uncertainty about the size of the population at risk of VTE.

For chapters 23 to 40 on surgical and trauma patients go to volume 2 of the full guideline.

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