National Institute for Health and Care Excellence

Final

# Venous thromboembolism in over 16s

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

*NICE guideline NG89 (volume 2)*

*Methods, evidence and recommendations*

*March 2018*

*Final*

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

## Update information

**August 2019:** Recommendation 1.12.11 was amended to clarify when anti-embolism stockings can be used for VTE prophylaxis for people with spinal injury.

**March 2018:** New recommendations were added on risk assessment for venous thromboembolism (VTE) and reducing the risk of VTE. These recommendations are marked as **[2018]**.

Some changes were made to clarify recommendation wording without an evidence review. These recommendations are marked as **[2010, amended 2018]**.

Recommendations are marked as **[2010]** when the evidence was last reviewed in 2010.

**Minor changes since publication**

**September 2025:** In recommendations 1.1.2 and 1.1.5 in the section on risk assessment, we highlighted the need to assess people for the risk of VTE and bleeding if they have been in accident and emergency for 12 hours or more. We also changed 'admission' to 'decision to admit' in recommendations 1.1.4 and 1.1.7.

**March 2025:** We updated links to relevant technology appraisal guidance in the sections on elective hip replacement and elective knee replacement.

**May 2021:** Recommendation 1.9.1 was amended to clarify that the Department of Health tool is commonly used to develop a treatment plan.

**January 2021:** Recommendations 1.1.2 and 1.1 5 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:** In recommendation 1.3.5 the British Standards for anti-embolism hosiery were updated because BS 6612 and BS 7672 have been withdrawn.

For the current recommendations, see www.nice.org.uk/guidance/ng89

**Disclaimer**

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

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

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# 23 Anaesthesia

## 23.1 Introduction

Anaesthesia is required for most operations and many investigations and other procedures. A general anaesthetic results in a patient losing consciousness. A regional anaesthetic technique involves injecting local anaesthetic into the epidural space (an epidural anaesthetic) or the subarachnoid space (a spinal anaesthetic) to achieve a sensory and/or motor block of the required area[a]. Other drugs such as opioids may be added to the local anaesthetic agents or used as sole agents. Spinal injections are usually given as a single dose with a limited duration of action. Epidural anaesthesia may be continued for hours or days by placing additional medication through a catheter left in the epidural space. Regional techniques may be combined with sedation or a general anaesthetic. Certain procedures such as caesarean section, some urological operations or orthopaedic procedures on the lower limbs, are well suited to the use of regional techniques. Other procedures such as intracranial neurosurgery are not suitable. The use of regional anaesthesia is rare in cardiac surgery but may be used for thoracic and vascular operations.

A concern with regional anaesthesia is that when neuroaxial blockades are used, thromboprophylaxis agents will increase the risk of spinal haematoma. Therefore, the timing of the use drugs that affect haemostasis or platelet function should be carefully planned.

## 23.2 Clinical evidence on anaesthesia

### 23.2.1 Regional vs. general anaesthesia

We identified one systematic review of 11 RCTs of regional vs general anaesthesia[256] and four additional RCTs giving a total of 15 studies with 1115 participants (Evidence Table H.20.1, appendix H). Twelve studies were in elective orthopaedic surgery patients, two urological and one in general surgery patients. Eleven studies used an epidural regional anaesthetic and four administered a spinal anaesthetic. Eight of the 11 studies using epidural anaesthesia continued the anaesthetic into the post-operative period for pain relief (in the remaining three studies the duration of the epidural anaesthetic was either unclear or not reported). In seven studies patients were given no prophylaxis for VTE, patients wore stockings in three studies, and received a pharmacological method of prophylaxis in five studies.

[a] The committee note the following edit to the definition for regional and local anaesthesia in the introduction:

'A regional anaesthetic technique involves injecting local anaesthetic to achieve a sensory and/or motor block of the required area. Regional anaesthesia may include:

1. Central neuro-axial (CNA) blockade (which includes spinal, epidural and combined spinal and epidural (CSE) anaesthesia).
2. Peripheral regional nerve block (which includes single shot techniques and continuous blockade using indwelling catheters).

Local anaesthesia involves the local infiltration of anaesthetic to achieve a sensory and/or motor block of a more local area.'

Nine studies were conducted in the 1980s and six in the 1990s, with the most recent trial published in 1996. It should be noted that general anaesthetic techniques and other aspects of perioperative management have changed considerably over this period.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

**Effect on DVT:** A significant risk reduction for DVT was found in patients receiving regional compared with general anaesthesia (38%) (RR=0.62, 95% CI: 0.53 to 0.73,15 studies) (Forest Plot 183, appendix L.20.1).

**Effect on pulmonary embolism:** Regional anaesthesia was significantly more effective in reducing risk of pulmonary embolism than general anaesthesia, with an overall reduction of 43% (RR=0.57, 95% CI: 0.35 to 0.91) (Forest Plot 184, appendix L.20.1).

**Effect on major bleeding**: Seven studies measured major bleeding events. Only one study reported an event, (RR=0.10, 95% CI: 0.01 to 1.71). The difference was not significant (Forest Plot 186, appendix L.20.1).

### 23.2.2 Subgroup analysis of epidural vs spinal anaesthesia

We found no RCTs comparing spinal and epidural anaesthesia with regard to the development of post-operative VTE. A subgroup analysis of the regional vs general anaesthesia RCTs was carried out to look for a difference in the magnitude of effect based on whether spinal or epidural regional anaesthesia was used. Eleven studies used epidural and four studies used spinal regional anaesthesia.

For deep vein thrombosis, a random effects meta-analysis was used, due to the heterogeneity within the results. Subgroup analyses were not possible for proximal DVT and major bleeding as there were no studies using spinal anaesthesia that assessed these variables.

**Effect on DVT:** A significantly reduced risk of DVT was found with both epidural compared with general anaesthesia (RR=0.62, 95% CI: 0.51 to 0.75, 11 studies) and spinal compared with general anaesthesia (RR=0.63, 95% CI:  0.48 to 0.83, 4 studies). No significant difference in the magnitude of effect between epidural and spinal anaesthesia was found (Chi-square on 1 df = 0.03, p=0.86) (Forest Plot 187, appendix L.20.2).

**Effect on pulmonary embolism:** We found a significantly reduced risk with epidural compared to general anaesthesia (RR=0.61, 95% CI: 0.38 to 0.99, 5 studies). There was a significant difference in risk of developing pulmonary embolism in a comparison of spinal vs general anaesthesia (RR=0.47, 95% CI: 0.23 to 0.96). There was no significant difference in the magnitude of effect between epidural and spinal anaesthesia Chi-square on 1 df = 0.42, p=0.52) (Forest Plot 188, appendix L.20.2).

### 23.2.3 Regional and general anaesthesia vs general anaesthesia only

One study in the systematic review mentioned above[256] and one further study[69] compared the combined use of regional anaesthesia and general anaesthesia with general anaesthesia alone (Evidence Table H.20.2, appendix H). One study[69] was in elective hip surgery patients. All patients received vitamin K antagonists for VTE prophylaxis. Patients receiving regional anaesthesia had an epidural for the duration of surgery only. The study was small, with only 37 patients. The second study[142] was of general surgery (elective gall bladder) patients. No VTE

prophylaxis was given to patients in the study. For regional anaesthesia patients, the epidural was prolonged into the post-operative period for pain relief. The studies did not report major bleeds or pulmonary embolism. One study[69] reported the site of deep vein thrombosis. No patient had a DVT that was situated above the knee and therefore the relative risk of proximal DVT was not estimable.

**Effect on DVT:** No significant difference was found (RR=0.69, 95% CI: 0.26 to 1.82, two studies) (Forest Plot 189, appendix L.20.3).

### 23.2.4 Risk of haematoma in anticoagulated patients receiving a regional anaesthetic

Risk of haematoma at the injection site is increased with the concomitant use of pharmacological prophylaxis agents. Removal of epidural catheter in the anticoagulated patient has also been associated with the development of spinal haematoma. The consequences of an epidural haematoma may be permanent paralysis below the level of the haematoma. The diagnosis is difficult as patients may have weakness or block because of the effects of the epidural. It would be extremely difficult to determine the true incidence as a randomised study would require very large numbers of patients due to the rarity of the event, however it has been estimated to be about 1 in 150,000 epidural blocks and 1 in 220,000 spinal anaesthetics.[40]

## 23.3 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

## 23.4 Recommendations and link to evidence

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| **Recommendation** | **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]** |
| **Relative values of different outcomes** | The outcomes considered were 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 benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. The timing of when pharmacological prophylaxis is started is particularly important because of the risk from bleeding. |
| **Economic considerations** | We found no evidence on the cost-effectiveness of regional anaesthesia compared with general anaesthesia in the context of VTE prophylaxis. However, there is a small body of literature that |

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| | shows regional anaesthesia to be associated with faster recovery time and reduced cost for some types of surgery.[215 ,311] This would suggest that, when it can be performed safely, regional anaesthesia is likely to be a highly cost-effective form of VTE prophylaxis. |
| **Quality of evidence** | All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).<br><br>Evidence from RCTs shows that regional anaesthesia compared with general anaesthesia reduces the risk of developing postoperative VTE. There was not enough evidence to determine differences in effect for major bleeding. |
| **Other considerations** | The evidence is limited to certain surgical procedures and there are other considerations involved when selecting an anaesthetic technique. Patient preferences are also an important consideration.<br><br>Regional anaesthesia alone should not be considered a suitable method of VTE prophylaxis. There are effective alternative techniques to prevent these complications and other matters to be taken into account when deciding on the most appropriate anaesthetic for a patient. In the absence of data on bleeding and the practical implications for different surgical procedures the guideline development group decided to recommend that its use be considered where practical in addition to other methods of prophylaxis.<br><br>Neuroaxial blockade should be avoided in those patients with significant bleeding disorders or receiving certain drugs that affect haemostasis or platelet function. The summary of product characteristics for each agent should be consulted for the latest guidance. |

### 1.1.1 Supporting recommendation based on Guideline Development Group consensus opinion

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| ***Recommendation*** | **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]** |
| **Trade off between clinical** | The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were |

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| **benefit and harms** | considered against the risk of major bleeding. An additional concern is the risk of developing an epidural haematoma as a result of the regional anaesthetic technique. Consequently, the Guideline Development Group recommends that the timing of pharmacological prophylaxis should be carefully planned to minimise the risk of spinal haematoma if a regional anaesthetic technique is used. Patients using antiplatelets or anticoagulant agents may be at increased risk of bleeding. |
| **Economic considerations** | We found no evidence on the cost-effectiveness of the timing of regional anaesthesia. However, it seems logical that the careful consideration of timing will improve the cost-effectiveness of regional anaesthesia. |
| **Other considerations** | The type of anticoagulant used may affect the timing of insertion and removal of the catheter. Such procedures should be delayed until the anticoagulant effect of the agent is minimal. For example, this may involve removing the catheter just before the next dose of thromboprophylaxis and delaying any further thromboprophylaxis for 2 hours after epidural catheter removal.<br><br>The requirements for each antiplatelet agent or anticoagulant will be different. The guideline development group recommends that clinicians refer to information within the summary of product characteristics for each agent and seek advice from experienced anaesthetists if uncertainty remains.<br><br>The balance of risks and benefits should be individualised for each patient and will depend on the type of regional anaesthesia, patient risk factors (including bleeding risks), and the type and dose of anticoagulant or use of other drugs affecting haemostasis or platelet function. An additional concern is the risk of developing an epidural haematoma as a result of a regional anaesthetic technique. |

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| **Recommendation** | **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]** |
| **Trade off between clinical benefit and harms** | The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. |
| **Economic considerations** | None |

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| **Other considerations** | The guideline development group decided that although a risk assessment for VTE should still be required upon admission to hospital, patients undergoing minor procedures under local anaesthesia without reduced mobility were likely to be at a low risk of VTE and as such routine prophylaxis was not likely to be beneficial. |

# 24 Lower limb immobilisation

## 24.1 Introduction

The use of lower limb immobilisation techniques in trauma and elective orthopaedic surgery affects a significant number of patients. The populations involved include trauma patients who do not require surgery, trauma patients who have had operative fixation, and elective cases usually involving the knee, foot and ankle. Immobilisation (such as with a plaster cast or brace) may be used for 3 months or more following the intervention. Certain groups may be at greater risk for VTE, for example patients undergoing conservative or operative treatment for rupture of the tendoachilles and patients undergoing more complex procedures with longer immobilisation.

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

For full details see review protocol in appendix C.

**Table 1: PICO characteristics of review question**

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| **Population** | Adults and young people (16 years and older) with lower limb immobilisation who are:<br>• Admitted to hospital<br>• Having day procedures<br>• Outpatients post-discharge<br><br>Immobilisation is defined as any clinical decision taken to manage the affected limb in such a way as to prevent normal weight bearing status and/or use of that limb. |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to |

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| | maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300mg)*<br><br>*off-label |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Unplanned return to theatre (up to 45 days from hospital discharge) |

| Study design | Randomised controlled trials (RCTs), systematic reviews of RCTs |
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## 24.3 Clinical evidence

Twelve studies were included in the review[41,77,78,155,168,172,178,179,185,263,269,301]; these are summarised in Table 2 below. Six studies were included from the previous guideline (CG92) [155,168,172,178,179,185]. Six studies were added in the update[41,77,78,263,269,301]. Evidence from these studies is summarised in the clinical evidence summary below (Table 3, Table 4, Table 5, Table 6). 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.

The included studies cover a heterogeneous population of surgically and non-surgically treated patients with injuries as diverse as simple ankle fractures to those with Achilles tendon ruptures. The evidence features a number of different immobilisation techniques (for example plaster cast or brace), and there is large variation in the duration of immobilisation, ranging from 2 weeks to 6 weeks.

**Table 2: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Bruntink 2017 PROTECT trial[41] | Intervention (n=154): LMWH, standard dose (nadroparin, 0.3ml). For the duration of immobilisation, mean (SD) 40.2 (8.5) days<br><br>Intervention (n=157): Fondaparinux 2.5mg. For the duration of immobilisation, mean (SD) 38.0 (8.7) days<br><br>Comparison (n=156): no VTE prophylaxis. For the duration of immobilisation, mean (SD) 40.3 (8.6) days | n=467<br><br>People with a fracture of the ankle or foot who required non-surgical treatment with immobilisation in a below-knee plaster cast for a minimum of four weeks.<br><br>Adults (mean age LMWH 47.7, fondaparinux 49.7, control 44.5)<br><br>Male to female ratio 118:160<br><br>The Netherlands | DVT (40 days): verified by duplex sonography<br><br>PE (40 days): verified by CT angiography<br><br>Major bleeding (40 days): no definition | |
| Domeij-arverud 2013[78] | Intervention (n=14): IPCD, foot. Fitted unilaterally beneath plaster cast. Duration 2 weeks post-op | n=26<br><br>People with plaster cast due to acute unilateral tendo Achilles rupture after open TA repair | DVT (42 days): confirmed with colour Doppler sonography | |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison (n=12): no VTE prophylaxis | Adults (mean age intervention 39.8, control 40.4; range 27-50 years)<br><br>Male to female ratio 1:1<br><br>Sweden | | |
| Domeij-arverud 2015[77] | Intervention (n=74): IPCD, calf. Fitted bilaterally, beneath plaster cast on operated leg. Duration 2 weeks post-op<br><br>Comparison (n=74): no VTE prophylaxis | n=148<br><br>People with plaster cast due to acute unilateral tendo Achilles rupture<br><br>Adults (mean 40.9 years; range 26-62)<br><br>Male to female ratio 88:21<br><br>Sweden | PE (42 days): CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography<br><br>DVT (42 days): in operated leg confirmed by compression duplex ultrasound | |
| Jorgense n 2002 [155] | Intervention (n=148): LMWH, standard dose (tinzaparin 3500U). Self-injected into abdominal wall once daily until plaster cast removed. Mean duration 5.5 weeks.<br><br>Comparison (n=152): no VTE prophylaxis | n=300<br><br>People with below knee plaster casts on lower extremity. Reasons for plaster cast: fracture 73.3%, tendon rupture 20.3%, other 6.3%<br><br>Adults (>18 years; mean 49 years)<br><br>Male to female ratio 128:172<br><br>Denmark | PE (mean 38 days): method of confirmation not reported<br><br>DVT (mean 38 days): diagnosed by ascending unilateral venography when plaster cast removed | Included in CG92 |
| Kock 1995 [168] | Intervention (n=176 analysed): LMWH, standard dose (certoparin 3000U) until cast removed (mean immobilisation time 15 days [sd 12, no range reported])<br><br>Comparison (n=163 | n=428<br><br>People with plaster cast (below knee 85.5%, above knee 14.55%). Reason for plaster cast: Grade II sprains and bruises 28.5%, Grade III sprains 30.4%, fractures 16.8%, other 3.5%<br><br>Adults (mean intervention 34.1 years, comparison 33 years; range 18-63 years) | DVT (until plaster cast removed). Confirmed by venography when plaster cast removed<br><br>Major bleeding (until plaster cast removed): no definition reported | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | analysed): no VTE prophylaxis. (mean immobilisation time 18 days [sd 13, range 2-72 days]) | Male to female ratio 208:131<br><br>Germany | | |
| Kujath 1993 [172] | Intervention (n=126):<br>LMWH, standard dose (nadroparin, 0.3ml). Started on first day of treatment, continued until plaster cast removed (mean 15.6 [6.8] days, range 7-41)<br><br>Comparison (n=127): no VTE prophylaxis. Mean period of plaster cast 15.8 [9.6] days, range 5-66) | n=306<br><br>People with plaster cast. Reason for plaster cast: soft tissue injury 70%, fractures 30%<br><br>Young people (aged >16 years; mean intervention 32.9±13.8, comparison 35.6±14.6<br><br>Male to female ratio 146:107<br><br>Germany | DVT (until plaster cast removed): diagnosed by ultrasound confirmed by venography | Included in CG92 |
| Lapidus 2007A [178] | Intervention (n=52):<br>LMWH, standard dose (Dalteparin 5000U). Started within hours post-surgery, up to 6th week, or mobilisation<br><br>Comparison (n=53):<br>No VTE prophylaxis (placebo) | n=105<br><br>People with below knee plaster cast due to Achilles tendon rupture<br><br>Adults (mean 40 years, range 18-75)<br><br>Male to female ratio 83:22<br><br>Sweden | All-cause mortality (42 days)<br><br>PE, fatal (42 days): method of confirmation not reported<br><br>PE (42 days) : method of confirmation not reported<br><br>DVT (42 days): confirmed by unilateral ascending phlebography of the affected legs, or colour duplex sonography (CDS) when phlebography fails at the 3rd week and 6th week, on the last day of the dose (or a day after), and when thrombosis is suspected, whichever earlier<br><br>Major bleeding (42 days): requiring blood transfusion/ surgery, or at a critical site such as intracranial, intraocular, intraspinal, or retroperitoneal | Included in CG92 |
| Lapidus 2007B[179] | Intervention (n=136): | n=272 | All-cause mortality (42 days) | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | LMWH, standard dose (Dalteparin 5000U). Started within hours post-surgery, up to 6th week, or mobilisation<br><br>Comparison (n=136):<br>No VTE prophylaxis (placebo) | People with lower limb immobilisation (82% plaster cast, 18% orthosis), due to acute ankle fracture<br><br>Adults (mean years 48, range 18-76)<br><br>Male to female ratio 124:148<br><br>Sweden | PE, fatal (42 days): method of confirmation not reported<br><br>PE (42 days): confirmed by: ventilation perfusion scan or spiral CT if suspected<br><br>DVT (42 days): screened for by unilateral ascending phlebography of the affected legs, or colour duplex sonography (CDS) when phlebography fails at 2nd and 6th week, on the last day of the dose (or a day after), and when thrombosis is suspected, whichever earlier<br><br>Major bleeding (42 days): requiring blood transfusion/ surgery, or at a critical site such as intracranial, intraocular, intraspinal, or retroperitoneal | Both groups received LMWH for one week prior to randomisation. |
| Lassen 2002 [185] | Intervention (n=217): LMWH, standard dose (reviparin 1750U). Mean duration of immobilisation: 43 days.<br><br>Comparison (n=223): no VTE prophylaxis. Mean duration of immobilisation: 44 days. | n=440<br><br>People with plaster cast (84.3%) or brace, due to fracture of leg (80%) or rupture of Achilles tendon (20%)<br><br>Adults (median 47 years; range 37-55)<br><br>Male to female ratio 112:105<br><br>Denmark | DVT (until plaster cast removed): diagnosed by unilateral venography within a week of plaster cast removal<br><br>PE (until plaster cast removed): confirmed by ventilation perfusion scanning<br><br>Major bleeding (until plaster cast removed): defined as clinically apparent bleeding associated with a decrease of at least 2.0g per deciliter in the haemoglobin level, requirement for transfusion of at least 2 units of packed red cells, or retroperitoneal or intracranial bleeding or other bleeding that investigators decided required permanent discontinuation of treatment | Included in CG92<br><br>Some patients (31%) who underwent surgery had heparin treatment up to 4 days before randomisation. |
| Samama 2013[263] | Intervention 1 (n=675): Fondaparinux 2.5mg (or 1.5mg in people with a calculated creatinine clearance between 30- | n=1349<br><br>People with lower limb immobilisation (plaster cast 83.8%, brace 6.2%, other 10%), due to non-surgical, unilateral single or multiple below-knee injury including: | All-cause mortality (21-45 days)<br><br>PE (21-45 days): confirmed by CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography | |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | 50mL min-1). Duration 21-45 days (until mobilisation). Mean duration of immobilisation 33.5 (9.4) days.<br><br>Intervention 2 (n=674): LMWH, standard dose (nadroparin 2850 units). Duration 21-45 days (until mobilisation). Mean duration of immobilisation 33.9 (9.0) days.<br><br>Concurrent medication: Free to take acetaminophen as needed. Use of aspirin or NSAIDs was allowed but discouraged | Fracture (most commonly concerning the external malleolus and the metatarsus) 89%; Achilles tendon rupture 2%; Other injury 11%<br><br>Adults (≥18 years; mean 46)<br><br>Male to female ratio 1:1<br><br>Multicentre international | DVT (21-45 days): confirmed by ultrasongraphy<br><br>Major bleeding (21-45 days): overt and fatal, occurred in a critical organ, was associated with a fall in haemoglobin concentration ≥2g dL-1, or led to a transfusion ≥2 units of packed red blood cells or whole blood<br><br>Clinically-relevant major bleeding (21-45 days): bleeding not qualifying as major, including bleeding leading to treatment discontinuation, gastrointestinal bleeding, haemoptysis, cutaneous hematoma >100cm2, epistaxis >5 minute, recurrent or leading to intervention, spontaneous macroscopic haematuria >24 hour<br><br>Heparin-induced thrombocytopaenia (21-45 days) | |
| Selby 2015[269] | Intervention (n=134): LMWH, standard dose (dalteparin 5000U). Duration 2 weeks. Mean immobilisation duration 44 (26) days.<br><br>Comparison (n=131): no VTE prophylaxis. Mean immobilisation duration 42 (29) days.<br><br>Concurrent medication: Aspirin and other | n=265<br><br>People with lower limb immobilisation in cast or splint (98.1%) due to unilateral (97.4%) or bilateral, closed or open fractures of the tibia, fibula, or ankle requiring surgical repair<br><br>Adults (mean 48 years; range 18-87<br><br>Male to female ratio 139:126<br><br>Canada | PE (90 days): confirmed by positive spiral computed tomography pulmonary angiogram, high probability V/Q lung scan, or leg imaging<br><br>DVT (90 days): confirmed by bilateral Doppler ultrasound<br><br>Major bleeding (90 days): defined as overt bleeding that was fatal, life threatening or involved a critical organ or major join, required surgical intervention, transfusion of 1 or more units of blood cells within 48 hours or the bleeding event, or was associated with a drop in haemoglobin of at least 20g/L within 48 hours of the bleeding event<br><br>Heparin-induced thrombocytopaenia (90 days) | |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | antiplatelet agents were allowed if they had been used before the injury for cardiac or stroke prophylaxis. Nonsteroidal anti-inflammatory agents were allowed | | | |
| van Adrichem 2016 POT-CAST trial [301] | Intervention (n=719): LMWH, standard dose (dalteparin 2500 IU or nadroparin 2850 IU if 100kg or less, and a double dose if over 100kg. Duration during immobilisation. Mean immobilisation duration 4.9 (2.5) weeks.<br><br>Comparison (n=131): no VTE prophylaxis. Mean immobilisation duration 4.9 (2.5) weeks.<br><br>Concurrent medication: none reported | n = 1435<br><br>Patients who were treated with casting of the lower leg. Indication for casting: Fracture 89%, Achilles' tendon rupture 7%, ankle distortion 2%, antalgic gait 1%, contusion 1%<br><br>Adults mean age (SD): LMWH 46.5 (16.5); no prophylaxis 45.6 (16.4) years<br><br>Male to female ratio 716/719<br><br>The Netherlands | PE (3 months): not defined<br><br>Symptomatic DVT (3 months): not defined<br><br>Major bleeding (3 months): not defined<br><br>Clinically relevant non-major bleeding (3 months): not defined | |

**Table 3: Clinical evidence summary: IPCD (below knee) 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 IPCD (below knee) versus no VTE prophylaxis (95% CI) |
| PE | 140 (1 study) 41 days | VERY LOW[b,c] due to risk of bias, imprecision | Not estimable | See comment [d] | 0 fewer per 1000 (from 30 fewer to 30 more)[a] |
| DVT | 162 (2 studies) 42 days | VERY LOW[b,c] due to risk of bias, imprecision | RR 1.19 (0.88 to 1.61) | 470 per 1000 | 89 more per 1000 (from 56 fewer to 287 more) |

a Risk difference calculated manually in RevMan
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
d Zero events in both arms

**Table 4: Clinical evidence summary: LMWH (standard 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 Control | Risk difference with LMWH (standard dose) versus no VTE prophylaxis (95% CI) |
| All-cause mortality | 377 (2 studies) 42 days | VERY LOW[b,c] due to risk of bias, imprecision | Not estimable | See comment [e] | 0 fewer per 1000 (from 10 fewer to 10 more)[a] |
| Fatal PE | 582 (3 studies) 38-42 days | VERY LOW[b,c] due to risk of bias, imprecision | Not estimable | See comment [e] | 0 fewer per 1000 (from 10 fewer to 10 more)[a] |
| PE | 2899 (7 studies) | VERY LOW[b,c,d] | Peto OR 0.37 | 6 per 1000 | 4 fewer per 1000 (from 5 fewer to 1 more) |

| 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 VTE prophylaxis (95% CI) |
| | 38-40 days | due to risk of bias, indirectness, imprecision | (0.12 to 1.14) | | |
| DVT | 1934 (8 studies) 38-40 days | MODERATE[b] due to risk of bias | RR 0.53 (0.41 to 0.68) | 152 per 1000 | 71 fewer per 1000 (from 49 fewer to 90 fewer) |
| Major bleeding | 2761 (6 studies) 38-90 days | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 1.99 (0.21 to 19.23) | 1 per 1000 | 1 more per 1000 (from 1 fewer to 13 more) |
| Heparin-induced thrombocytopaenia | 258 (1 study) 90 days | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 0.98 (0.06 to 15.83) | 8 per 1000 | 0 fewer per 1000 (from 7 fewer to 103 more) |
| Clinically relevant non-major bleeding | 1435 (1 study) 38 days | VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision | Peto OR 7.36 (0.15 to 370.84) | 0 per 1000 | 0 more per 1000 (from 2 fewer to 5 more)a |

a Risk difference calculated manually 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
d Downgraded by 1 or 2 increments due to intervention indirectness because the majority of the evidence was from a study that had mixed standard or high doses of LMWH
e Zero events in both arms

**Table 5: Clinical evidence summary: Fondaparinux versus LMWH (standard prophylactic dose)**

| 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 Fondaparinux versus LMWH (standard dose) (95% CI) |
| All-cause mortality | 1243 (1 study) 21-45 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.4 (0.15 to 372.99) | 0 per 1000 | -[c] |
| PE | 1429 (2 studies) 21-45 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.41 (0.46 to 118.65) | 0 per 1000 | -[c] |
| DVT | 1351 (2 studies) 21-45 days | MODERATE[a] due to risk of bias | RR 0.27 (0.15 to 0.51) | 65 per 1000 | 47 fewer per 1000 (from 32 fewer to 55 fewer) |
| Major bleeding | 1528 (2 studies) 21-45 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.35 (0.15 to 370.19) | 0 per 1000 | -[c] |
| Clinically relevant non-major bleeding | 1344 (1 study) 21-45 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.36 (0.05 to 2.6) | 4 per 1000 | 3 fewer per 1000 (from 4 fewer to 7 more) |
| Heparin-induced thrombocytopaenia | 1344 (1 study) 21-45 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.13 (0 to 6.78) | 1 per 1000 | 1 fewer per 1000 (from 1 fewer to 9 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 Absolute effects could not be calculated due to zero events in the control arm

**Table 6: Clinical evidence summary: Fondaparinux 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 Fondaparinux versus no VTE prophylaxis (95% CI) |
| PE | 186 (1 study) 40 days | VERY LOW[a] due to risk of bias, imprecision | Peto OR 0.14 (0.01 to 2.2) | 21 per 1000 | 18 fewer per 1000 (from 21 fewer to 24 more) |
| DVT | 186 (1 study) 40 days | MODERATE[c] due to risk of bias | RR 0.09 (0.01 to 0.71) | 117 per 1000 | 106 fewer per 1000 (from 34 fewer to 116 fewer) |
| Major bleeding | 186 (1 study) 40 days | MODERATE[c] due to risk of bias | Not estimable | See comment [d] | 0 fewer per 1000 (from 20 fewer to 20 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 Risk difference calculated manually in Review Manager
c 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
d Zero events in both arms

## 24.4 Economic evidence

### Published literature

No relevant health economic studies were identified.

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

## 24.5 Evidence statements

### Clinical

Very low quality evidence from one study showed no difference in PE rates between IPCD and no prophylaxis, however there was uncertainty around this result. Very low quality evidence from two studies suggested an increased DVT risk when using IPCD although there was serious imprecision around this effect estimate indicating that the true effect could be consistent with no clinical difference.

When comparing either LMWH or Fondaparinux with no prophylaxis, moderate quality evidence showed that both LMWH (8 studies) and Fondaparinux (1 study) provided a clinically important reduction in DVT compared to no prophylaxis. In head to head comparisons, moderate quality evidence from 2 studies showed a benefit for fondaparinux over LMWH with a clinically important reduction in DVT. However on the basis of very low quality evidence, no clinical difference was observed for all other critical outcomes (all-cause mortality, fatal PE, PE and major bleeding) when comparing LMWH, fondaparinux, or no prophylaxis. There was very serious imprecision associated with all of the outcomes apart from DVT.

### Economic

No relevant economic evaluations were identified.

## 24.6 Recommendations and link to evidence

| **Recommendations** | **1.5.4 Consider pharmacological VTE prophylaxis with LMWH[b] or fondaparinux sodium[c] 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]** |
|---|---|
| **Research recommendation** | **6. What is the clinical and cost effectiveness of direct oral anticoagulants (DOACs) for preventing VTE in people with lower limb immobilisation?** |
| 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 |

[b] 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.

[c] 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.

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| | to 45 days from hospital discharge) as critical outcomes.<br><br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br><br>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 majority of the evidence is of very low quality due to high risk of bias and imprecision around the effect estimates. One study also provided indirect evidence due to a mix of standard and high doses of LMWH being used.<br><br>For the comparison between IPCD and no prophylaxis, the evidence for both DVT and PE was all of very low quality. For the comparison between LMWH and no prophylaxis, and for the comparison of fondaparinux with LMWH, all the evidence was of very low quality except for the DVT outcome where the evidence was of moderate quality (no imprecision). |
| Trade-off between clinical benefits and harms | The use of lower limb immobilisation following trauma and elective orthopaedic surgery affects a significant number of patients. This is also highly heterogeneous group of patients, represented by a wide variation of DVT rates reported in the no prophylaxis arms. The studies included both patients admitted for their trauma and those treated and discharged in the trauma department.<br><br>Based on the clinical evidence presented, no clinically important difference was found between IPCD and no prophylaxis. Due to the imprecision associated with the results, the committee considered that the evidence base was not strong enough in this context to recommend IPCD in this population.<br><br>LMWH showed a clinically important reduction in DVT. There was also a suggested reduction in PE and increase in major bleeding, however these differences were too small to be considered clinically important and there was considerable uncertainty around the results.<br><br>Fondaparinux also showed a clinically important reduction in DVT alongside a suggested decrease in PE, although this second finding was very imprecise and no major bleeding events were noted in either group. The studies comparing fondaparinux versus LMWH (standard dose) also showed a clinically important reduction in DVT when using fondaparinux compared to LMWH. However the point estimates for all-cause mortality and major bleeding all favoured LMWH, but these findings did not reach clinical importance and there was uncertainty around the effect. The committee considered that overall the evidence did not support one treatment over another, therefore either should be recommended for those at high risk of VTE in the population with lower limb immobilisation.<br><br>There is a range of procedures and injuries which require the application of lower limb immobilisation. The length of the immobilisation/cast and the location of injury within the leg may also differ. The committee recognised that baseline mobility can be difficult to assess and that the risk of VTE associated with lower limb immobilisation is most easily defined by the duration of immobilisation. The committee decided to recommend prophylaxis for 42 days based on the lower limb immobilisation information provided within the trials included in this evidence review. Most patients are expected to remain mobile (although not weight bearing on the affected limb), while others may remain immobile, generally. These are the factors which may put patients at different levels of risk.<br><br>The committee acknowledged that for the subgroup of patients with tendo-Achilles rupture, who are at higher risk of VTE, prophylaxis should be offered. The 'consider' recommendation is a reflection of the very low to moderate quality evidence. However, it is the committee's belief that for this group of patients, prophylaxis with LMWH (standard dose) is likely to be most clinically and cost effective compared |

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| | with subgroups with ankle fractures (whether operated or not operated on) and soft tissue injuries. |
| Trade-off between net clinical effects and costs | No relevant economic studies were identified for this review. Unit costs were presented to the committee for discussion alongside the clinical evidence.<br>The committee discussed the duration of prophylaxis and acknowledged that in this population, the cost of prophylaxis is likely to be higher compared to other populations due to the longer duration for which prophylaxis is required, which ranges from 2 to 6 weeks. The committee acknowledged that durations of immobilisation that are longer than 6 weeks are likely to be rare. Prescribing pharmacological prophylaxis for these long durations will need to be decided on an individual basis, balancing the risk of VTE with the risk of bleeding.<br>The committee considered that LMWHs and fondaparinux are the only interventions with clinical evidence that show clinical benefit in terms of DVT prevention to support a recommendation. Studies that compared LMWH with fondaparinux suggested a clinical benefit for fondaparinux over LMWH for the outcome of DVT, but less clear evidence of benefit for other critical outcomes. Given the higher cost of fondaparinux (£4.4 per day compared to a range of £2.77 to 3.03 for LMWHs) it was considered that it may not be as cost-effective as LMWH but that it could be recommended as an option; as some individuals would have contraindications to LMWHs. The committee acknowledged that in current practice clinicians usually default to using LMWH, unless there are contraindications. |
| Other considerations | The committee noted that these recommendations apply to all patients who are immobilised by a cast or brace and that includes patients: admitted to hospital for treatment, treated as day procedures and those treated as outpatients in the trauma department and discharged straight after. The higher risk patients are likely to be those admitted for their treatment but this is not clear from the evidence and therefore the recommendation applies to all patients.<br>The committee noted the lack of evidence for the clinical and cost-effectiveness of DOACs in this population (rivaroxaban, apixaban and dabigatran) and suggested a research recommendation would be beneficial looking at these interventions in comparison with LMWH and/or fondaparinux; see appendix R for more details. |

# 25 Fragility fractures of the pelvis, hip and proximal femur

## 25.1 Introduction

Fractures of the pelvis, hip and proximal femur are very common in the elderly population and carry a significant risk of morbidity and mortality. They occur mainly as osteoporotic or fragility fractures but a small proportion may result from major trauma in a younger age group. The latter is covered under the section on major trauma (chapter 34).

The risk of VTE in people with fragility fractures of the pelvis, hip or proximal femur can be quite high with an additional impact from common comorbidities such cardiovascular, respiratory and cerebrovascular disease.

Trauma and orthopaedic surgeons and orthogeriatricians recognise that people who sustain other fragility fractures of the lower limb, for example to the distal femur or tibia, are very similar to the population sustaining fragility fractures of the pelvis, hip and proximal femur. This review has been confined to a specific subgroup of this population due to difficulties in defining which injuries have a similar impact on patients' physiology and rehabilitation. Clinicians should interpret these recommendations more widely when considering how to manage VTE prophylaxis for people with similar major lower limb fragility fractures.

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

For full details see review protocol in appendix C.

**Table 7: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) with fragility fractures of the pelvis, hip or proximal femur who are:<br>• Admitted to hospital<br>• Outpatients post-discharge |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ dalteparin (standard prophylactic dose 5000 units once daily; |

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| | minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*)<br>○ 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*)<br><br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300mg)*<br>*off-label |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Infection (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

## 25.3 Clinical evidence

Sixteen studies were included in the review, fourteen studies were included in CG92; [85 89 90 94 107 129 154 174 218 220 221 248 285 ,324] and two new studies were identified; [114 287], these are summarised in Table 8 below. One study was published before CG92 [248] and was not previously included due to methodological concerns; it has now been included in this review.

One study that was previously included in CG92 has been excluded from this review and is now included in the major trauma review. [279]

Evidence from these studies is summarised in the clinical evidence summary below (Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, Table 16, Table 17, Table 18, Table 19, Table 20). 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 8: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Eriksson 2001 [85]: PENTHIFRA trial | Intervention (n=862):<br>LMWH, enoxaparin, 40mg once daily (standard dose) subcutaneously given along with placebo (saline). From 12±2 hours preoperatively and continued for 5-9 days.<br><br>Comparison (n=849):<br>Fondaparinux, 2.5mg, once daily, subcutaneously given along with placebo (saline). From 6±2 hours postoperatively and continued for 5-9 days. | n=1711<br><br>People undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck<br><br>Age (mean): 79 years<br>Gender (male to female ratio): 1:3<br><br>Argentina, Australia/New Zealand, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Norway, Poland, Portugal, Spain, South Africa, Sweden, Switzerland, the | All-cause mortality (49 days)<br><br>DVT (symptomatic and asymptomatic) (11 days): confirmed by systemic ascending bilateral contrast venography<br><br>PE (11 days): confirmed by high-probability lung scanning, pulmonary angiography, helical computed tomography | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Concomitant treatment:<br>AES was permitted, 49% of patients used AES. Early mobilisation was strongly recommended. | Netherlands, UK | Fatal PE (11 days): confirmed at autopsy<br><br>Major bleeding (11 days): defined as fatal bleeding, retroperitoneal, intracranial, or intraspinal bleeding, bleeding that involved any other critical organ, bleeding leading to reoperation, and overt bleeding with a bleeding index of 2 or more. | |
| Eriksson 2003A [89] | Intervention (n=327):<br>Fondaparinux sodium, 2.5 mg, once daily, subcutaneously given up to 6-8 days after surgery then an additional 19-23 days (extended duration), total duration of 25-31 days.<br><br>Comparison (n=329):<br>Fondaparinux sodium, 2.5 mg, once daily, subcutaneously given up to 6-8 days after surgery (standard duration). Followed by placebo, 0.5ml isotonic sodium chloride, once daily, subcutaneously for additional 19-23 days, total duration of 25-31 days.<br><br>Concomitant treatment:<br>AES was permitted, 46% of patients used AES. Early mobilisation was strongly recommended. | n=656<br><br>People undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck<br><br>Age (median): 79 years<br>Gender (male to female ratio): 1:2<br><br>Argentina, Australia, Belgium, Czech Republic, Denmark, Finland, France, Greece, Italy, Poland, Portugal, Spain, Sweden, Switzerland, the Netherlands, UK | All-cause mortality (25-32 days)<br><br>DVT (symptomatic and asymptomatic) (25-32 days): confirmed by systemic ascending bilateral contrast venography<br><br>PE (25-31 days): confirmed by high-probability lung scanning, pulmonary angiography, spiral computed tomography<br><br>Fatal PE (25-31 days): confirmed at autopsy<br><br>Major bleeding (25-31 days): defined as fatal bleeding, retroperitoneal, intracranial, or intraspinal bleeding, bleeding that involved any other critical organ, bleeding leading to reoperation, and | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | overt bleeding with a bleeding index of 2 or more. | |
| Eskeland 1966 [90] | Intervention (n=100): Vitamin K antagonists, phenindione, doses controlled by PP-test or Thrombotest three times a week, dose reduced gradually to zero from 7-14 days.<br><br>Comparison (n=100): Control group, no prophylaxis, no further details reported. | n=200<br><br>People admitted with sub-capital or pertrochanteric fracture of the femur<br><br>Age (mean): 76 years<br>Gender (male to female ratio): 1:5<br><br>Norway | All-cause mortality (90 days)<br><br>DVT (symptomatic and asymptomatic) (90 days): definition not reported<br><br>PE (90 days): definition not reported<br><br>Fatal PE (90 days): confirmed by necropsy | Included in CG92 |
| Fisher 1995 [94] | Intervention (n=145): IPCD, thigh-length, pressures varied from 25-45 mmHg according to location of the six chambers. Compression cycle was 71 seconds, each compression lasted 11 seconds.<br><br>Comparison (n=159): Control group, received same clinical care as the intervention group.<br><br>Concomitant treatment: Physiotherapy, active mobilisation regimen which started on postoperative day 1 | n=304<br><br>People admitted with pelvic, acetabular, femoral neck, intertrochanteric, or sub-trochanteric fractures<br><br>Age: 80% >40 years<br>Gender (male to female ratio): Not reported<br><br>Canada | DVT (symptomatic and asymptomatic) (mean: 14 days): confirmed by Doppler ultrasonography<br><br>PE (5-10 days): confirmed by ventilation perfusion (VQ) lung scan | Included in CG92 |
| Galasko 1976[107] | Intervention (n=50): Unfractionated heparin, 5000IU, twice daily, subcutaneously given on admission to hospital and continued until patient was discharged, transferred or fully mobilised (duration of hospital length of stay not | n=100<br><br>People who admitted for intertrochanteric or trans-cervical femoral fractures<br><br>Age (mean): not reported<br>Gender: 100% female<br><br>UK | All-cause mortality (time-point not reported)<br><br>DVT (symptomatic and asymptomatic) (time-point not reported): confirmed by venography | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | reported)<br><br>Comparison (n=50):<br>Control group, no prophylaxis (usual care) | | PE (time-point not reported): confirmed by clinical and radiological examinations or at autopsy<br><br>Wound infection/haematoma (time-point not reported) | |
| Goel 2009 [114] | Intervention (n=157)<br>LMWH, dalteparin, 5000IU, once daily (standard dose) subcutaneously given. 2500IU was administered subcutaneously two hours pre-operatively, followed by 2500IU eight hours post-operatively, and 5000IU on following days each morning up to and including the 14th day.<br><br>Comparison (n=148)<br>No prophylaxis, saline given subcutaneously once daily for 14 days | n=305<br><br>People admitted with unilateral isolated fractures below the knee which require operative fixation<br><br>Age (mean): 40.95 years<br>Gender (male to female ratio): 1.6:1<br><br>Canada | All-cause mortality (time-point not reported)<br><br>DVT (symptomatic and asymptomatic) (14 days): confirmed by bilateral venography<br><br>Major bleeding (time-point not reported): defined as fall in haemoglobin of ≥2 g/dl within a 24-hour period resulting in transfusion of ≥2 units of blood, intracranial, intraspinal, intra-ocular, retroperitoneal or pericardial bleeding, and causing death | New study |
| Hamilton 1970[129] | Intervention (n=38):<br>Vitamin K antagonist, phenindione, prothrombin time to 2-2.5 times the control (prothrombin time not reported). Duration of intervention not clearly reported.<br><br>Comparison (n=38):<br>Control group, no further details | n=76<br><br>People admitted for a hip fracture<br><br>Age (mean): 77 years<br>Gender (male to female ratio): 1:5<br><br>Canada | All-cause mortality (time-point not reported)<br><br>DVT (symptomatic and asymptomatic) (5-12 days): confirmed by ascending phlebography<br><br>Major bleeding (time-point not | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | reported. | | reported): patients requiring blood transfusions<br><br>Deep wound infection (time-point not reported) | |
| Jørgensen 1992[154] | Intervention (n=30):<br>LMWH, dalteparin, 5000IU (standard dose), subcutaneously given from 2 hours preoperatively. First and second injections contained 2500IU; second injection administered 12 hours postoperatively. 5000IU administered once daily thereafter for 6 days.<br><br>Comparison (n=38):<br>Placebo, isotonic sodium chloride, from 2 hours preoperatively. Second injection administered 12 hours postoperatively. Placebo administered once daily thereafter for 6 days. | n=68<br><br>People admitted for a hip fracture<br><br>Age (mean): 80 years<br>Gender (male to female ratio): 1:3<br><br>Denmark | All-cause mortality (84 days)<br><br>DVT (symptomatic and asymptomatic) (9 days): confirmed by $I^{125}$ fibrinogen uptake test and scans and ascending phlebography<br><br>PE (84 days): definition not reported<br><br>Superficial wound infection (84 days) | Included in CG92 |
| Lahnborg 1980 [174] | Intervention (n=71):<br>Unfractionated heparin, sodium heparin, 5000IU subcutaneously, every 12 hours for 10 days, started 2-3 hours after the operation.<br><br>Comparison (n=69):<br>Placebo, 0.5ml of 0.85% saline, subcutaneously every 12 hours for 10 days, started 2-3 hours after the operation | n=140<br><br>People admitted for nailing of a fractured neck of the femur<br><br>Age (mean): 77 years<br>Gender (male to female ratio): 1:2<br><br>Sweden | DVT (symptomatic and asymptomatic) (10 days): confirmed by $I^{125}$ fibrinogen uptake test and scans<br><br>PE (time-point not reported): 'diagnosed clinically' | Included in CG92 |
| Monreal 1989[218] | Intervention (n=46):<br>LMWH, dalteparin, 5000IU once daily (standard dose), subcutaneously given | n=90<br><br>People admitted for a hip fracture | All-cause mortality (time-point not reported)<br><br>PE (8 days): | |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | every evening for 9 days. 2500IU was administered 2 hours preoperatively. Placebo injections given in the evening.<br><br>Comparison (n=44):<br>Unfractionated heparin, 5000IU, subcutaneously given every 8 hours for 9 days | Age (mean): 77 years<br>Gender (male to female ratio): 1:5<br><br>Spain | confirmed by ventilation-perfusion lung scanning | |
| Morris 1976[220] | Intervention (n=80):<br>VKA, warfarin sodium, loading dose of 30mg within 24 hours of admission. No warfarin given next day, third day a thrombotest level was obtained. Dose adjusted to achieve modest degree of anticoagulation (a thrombotest level of 10%). Warfarin was continued until the patients was independently mobile or for 3 months.<br><br>Comparison (n=80)<br>Control group, no prophylaxis. No further details reported | n=160<br><br>People admitted to hospital with a fractured neck of femur (sub-capital or intertrochanteric)<br><br>Age (mean): 78.3 years<br>Gender (male to female ratio): 1:7<br><br>UK | All-cause mortality (90 days)<br><br>DVT (symptomatic and asymptomatic) (10 days): confirmed by $I^{125}$ fibrinogen uptake test and scans<br><br>PE (time-point not reported): confirmed by clinical signs, chest X-rays and electrocardiograms<br><br>Major bleeding (time-point not reported): definition not reported | Included in CG92 |
| Moskovitz 1978 [221] | Intervention (n=29):<br>Unfractionated heparin, sodium heparin, 5000IU subcutaneously given every 8 hours for 7 days. Patients wore AES (length unspecified), length of time AES worn for not reported.<br><br>Comparison (n=23):<br>Placebo, saline, subcutaneously given every 8 hour for 7 days. Patients wore | n=52<br><br>People admitted for a hip fracture<br><br>Age: 61% ≥70 years<br>Gender (male to female ratio): 1:2<br><br>USA | All-cause mortality (time-point not reported)<br><br>DVT (symptomatic and asymptomatic) (10 days): confirmed by $I^{125}$ fibrinogen uptake test and scans<br><br>PE (time-point not reported): confirmed by radionuclide perfusion lung- | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | AES (length unspecified), length of time AES worn for not reported. | | scanning<br><br>Major bleeding (time-point not reported): definition not reported<br><br>Fatal PE (time-point not reported): definition not reported | |
| Pulmonary Embolism Prevention Collaborative Group 2000: PEP trial [248] | Intervention (n=6679):<br>Aspirin, 160mg, orally once daily, for 35 days<br>44% also taking UFH or LMWH and 30% also wearing AES<br><br>Comparison (n=6677):<br>Placebo, orally once daily for 35 days<br>43% also taking UFH or LMWH and 29% also wearing AES | n=13356<br><br>People admitted for a femoral-neck fracture or other fracture of the proximal femur.<br><br>Age (mean): 79 years<br>Gender (male to female ratio): 1:4<br><br>Australia, New Zealand, South Africa, Sweden, UK | All-cause mortality (35 days)<br><br>PE (35 days): confirmed by pulmonary angiogram, a high-probability ventilation-perfusion scan and at necropsy.<br><br>Fatal PE (35 days): confirmed by necropsy<br><br>Wound infection (35 days) | New study<br><br>Additional heparin and stocking prophylaxis in some people in both the intervention and control groups.<br><br>Subgroup details provided in the paper are presented in the forest plots in appendix L for information only (not analysed due to not matching review protocol). |
| Svend-Hansen 1981 [285] | Intervention (n=65):<br>Unfractionated heparin, 5000IU, subcutaneously administered three times daily for 14 days.<br><br>Comparison (n=65):<br>Placebo, given for 14 days. | n=130<br><br>People admitted with proximal femoral fractures<br><br>Age (mean): 73 years<br>Gender (male to female ratio): 1:3<br><br>Denmark | All-cause mortality (time-point not reported)<br><br>DVT (symptomatic and asymptomatic) (14 days): confirmed by $I^{125}$ fibrinogen uptake test and scans | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | Fatal PE (time-point not reported): definition not reported | |
| Tang 2017 [287] | Intervention 1 (n=96): LMWH, enoxaparin, 40mg once daily (standard dose), subcutaneously given from 12 hours postoperatively for one week. Patients then received rivaroxaban, 10mg once daily, orally given for 28 days.<br><br>Intervention 2 (n=95): LMWH, enoxaparin, 40mg once daily (standard dose), subcutaneously given from 12 hours postoperatively, duration of intervention not clearly reported. Assumption that duration was 28 days was made.<br><br>Comparison (n=96): Rivaroxaban, 10mg, orally given from 6 hours postoperatively for 28 days<br><br>Concomitant treatment: All patients were encouraged to perform passive movement training of the affected limbs at day 2 after the surgery. | n=287<br><br>People admitted with hip fractures<br><br>Age (mean):<br>Gender (male to female ratio): 1:1.6<br><br>China | All-cause mortality (30 days)<br><br>DVT (symptomatic and asymptomatic) (30 days): confirmed by colour Doppler ultrasound. Doppler ultrasound was recommended for asymptomatic patients.<br><br>PE (30 days): confirmed by CT pulmonary angiogram (CTPA) when PE was suspected and/or confirmed.<br><br>Fatal PE (30 days): | New study |
| Xabregas 1978[324] | Intervention (n=25): Unfractionated heparin, calcium, adjusted by weight, 100IU/kg, | n=50<br><br>People admitted with a fractured neck of the femur | DVT (symptomatic and asymptomatic) (time-point not reported): confirmed by $I^{125}$ | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | subcutaneously administered three times daily for 14 days.<br><br>Comparison (n=25):<br>Placebo, saline solution, given for 14 days. | Age (mean): 76 years<br>Gender (male to female ratio): 1:3<br><br>Australia | fibrinogen uptake test and scans<br><br>PE (time-point not reported): definition not reported<br><br>Wound infection (time-point not reported) | |

**Table 9: 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 (standard dose) (95% CI) |
| All-cause mortality | 305 (2 studies) 84 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.17 (0.33 to 4.19) | 27 per 1000 | 5 more per 1000 (from 18 fewer to 86 more) |
| DVT (symptomatic and asymptomatic) | 305 (2 studies) 14 days | LOW[a,b] due to risk of bias, imprecision | RR 0.59 (0.37 to 0.96) | 242 per 1000 | 99 fewer per 1000 (from 10 fewer to 152 fewer) |
| PE | 68 (1 study) 84 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Peto OR 0.17 (0 to 8.65) | 26 per 1000 | 22 fewer per 1000 (from 26 fewer to 163 more) |
| Major bleeding | 237 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 20 fewer to 20 more)[d] |
| Wound infection | 68 (1 study) 84 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.27 (0.19 to 8.47) | 53 per 1000 | 14 more per 1000 (from 43 fewer to 393 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 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.

**Table 10: 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 (standard dose) (95% CI) |
| All-cause mortality | 90 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 0.64 (0.11 to 3.64) | 68 per 1000 | 25 fewer per 1000 (from 61 fewer to 180 more) |
| PE | 90 (1 study) 8 days | MODERATE[a] due to risk of bias | Peto OR 7.95 (1.53 to 41.29) | 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 the control arm

**Table 11: Clinical evidence summary: LMWH (standard dose; standard duration) versus fondaparinux**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux | Risk difference with LMWH (standard dose) (95% CI) |
| All-cause mortality | 1673 (1 study) 49 days | LOW[a] due to imprecision | RR 1.09 (0.71 to 1.67) | 46 per 1000 | 4 more per 1000 (from 13 fewer to 31 more) |
| DVT (symptomatic and asymptomatic) | 1247 (1 study) 11 days | MODERATE[b] due to risk of bias | RR 2.39 (1.75 to 3.28) | 79 per 1000 | 109 more per 1000 (from 59 more to 179 more) |
| PE | 1671 (1 study) 11 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.01 (0.06 to 16.13) | 1 per 1000 | 0 more per 1000 (from 1 fewer to 18 more) |
| Major bleeding | 1673 | | RR 1.04 | 22 per 1000 | 1 more per 1000 |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux | Risk difference with LMWH (standard dose) (95% CI) |
| | (1 study)<br>11 days | LOW[a]<br>due to imprecision | (0.55 to 1.97) | | (from 10 fewer to 21 more) |
| Fatal PE | 1671<br>(1 study)<br>11 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.99<br>(0.14 to 7.01) | 2 per 1000 | 0 fewer per 1000<br>(from 2 fewer to 14 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 12: LMWH (standard dose; standard duration) followed by rivaroxaban versus rivaroxaban**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Rivaroxaban | Risk difference with LMWH + rivaroxaban (95% CI) |
| All-cause mortality | 192<br>(1 study)<br>30 days | LOW[b]<br>due to imprecision | Peto OR 7.39<br>(0.15 to 372.38) | 0 per 1000 | -[a] |
| DVT (symptomatic and asymptomatic) | 192<br>(1 study)<br>30 days | VERY LOW[b,c]<br>due to indirectness, imprecision | RR 1.8<br>(0.63 to 5.17) | 52 per 1000 | 42 more per 1000<br>(from 19 fewer to 217 more) |
| PE | 192<br>(1 study)<br>30 days | LOW[b]<br>due to imprecision | RR 2<br>(0.18 to 21.69) | 10 per 1000 | 10 more per 1000<br>(from 9 fewer to 216 more) |
| Fatal PE | 192<br>(1 study)<br>30 days | LOW[b]<br>due to imprecision | Peto OR 7.39<br>(0.15 to | 0 per 1000 | -[a] |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Rivaroxaban | Risk difference with LMWH + rivaroxaban (95% CI) |
| | | | 372.38) | | |

a Absolute effects could not be calculated due to zero events in one of the arms.
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

**Table 13: LMWH (standard dose; standard duration) followed by rivaroxaban versus LMWH (standard dose; extended duration)**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH (extended duration) | Risk difference with LMWH + rivaroxaban (95% CI) |
| All-cause mortality | 192 (1 study) 30 days | VERY LOW[a,b] due to indirectness, imprecision | RR 0.99 (0.06 to 15.59) | 11 per 1000 | 0 fewer per 1000 (from 10 fewer to 154 more) |
| DVT (symptomatic and asymptomatic) | 191 (1 study) 30 days | VERY LOW[a,b] due to indirectness, imprecision | RR 0.74 (0.33 to 1.68) | 126 per 1000 | 33 fewer per 1000 (from 85 fewer to 86 more) |
| PE | 191 (1 study) 30 days | VERY LOW[a,b] due to indirectness, imprecision | RR 0.49 (0.05 to 5.37) | 21 per 1000 | 11 fewer per 1000 (from 20 fewer to 92 more) |
| Fatal PE | 191 (1 study) 30 days | VERY LOW[a,b] due to indirectness, imprecision | RR 0.99 (0.06 to 15.59) | 11 per 1000 | 0 fewer per 1000 (from 10 fewer to 154 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 outcome definition reported did not meet definition of outcome in protocol

**Table 14: LMWH (standard dose; extended duration) versus rivaroxaban**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Rivaroxaban | Risk difference with LMWH (extended duration) (95% CI) |
| All-cause mortality | 191 (1 study) 30 days | VERY LOW[a,b] due to indirectness, imprecision | Peto OR 7.47 (0.15 to 376.35) | 0 per 1000 | -[a] |
| DVT (symptomatic and asymptomatic) | 191 (1 study) 30 days | VERY LOW[a,b] due to indirectness, imprecision | RR 2.43 (0.89 to 6.62) | 52 per 1000 | 74 more per 1000 (from 6 fewer to 293 more) |
| PE | 191 (1 study) 30 days | VERY LOW[a,b] due to indirectness, imprecision | RR 2.02 (0.19 to 21.92) | 10 per 1000 | 11 more per 1000 (from 8 fewer to 218 more) |
| Fatal PE | 191 (1 study) 30 days | VERY LOW[a,b] due to indirectness, imprecision | Peto OR 7.47 (0.15 to 376.35) | 0 per 1000 | -[a] |

a Absolute effects could not be calculated due to zero events in one of the arms.
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

**Table 15: Clinical evidence summary: Fondaparinux (extended duration) versus fondaparinux (standard duration)**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux (standard duration) | Risk difference with Fondaparinux (extended duration) (95% CI) |
| All-cause mortality | 656 (1 study) | LOW[a] | RR 0.75 (0.26 to 2.15) | 24 per 1000 | 6 fewer per 1000 (from 18 fewer to 28 more) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux (standard duration) | Risk difference with Fondaparinux (extended duration) (95% CI) |
| | 25-31 days | due to imprecision | | | |
| DVT (symptomatic and asymptomatic) | 426 (1 study) 25-32 days | MODERATE[b] due to risk of bias | RR 0.04 (0.01 to 0.13) | 339 per 1000 | 326 fewer per 1000 (from 295 fewer to 336 fewer) |
| PE | 656 (1 study) 25-31 days | LOW[a] due to imprecision | Peto OR 0.14 (0.01 to 2.19) | 6 per 1000 | 5 fewer per 1000 (from 6 fewer to 7 more) |
| Major bleeding | 656 (1 study) 25-31 days | MODERATE[a] due to imprecision | RR 4.02 (0.86 to 18.81) | 6 per 1000 | 18 more per 1000 (from 1 fewer to 108 more) |
| Fatal PE | 656 (1 study) 25-31 days | LOW[a] due to imprecision | Peto OR 0.14 (0 to 6.9) | 3 per 1000 | 3 fewer per 1000 (from 3 fewer to 18 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 16: 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 | 230 (2 studies) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 1.76 (1.04 to 3.01) | 148 per 1000 | 112 more per 1000 (from 6 more to 297 more) |
| DVT (symptomatic and | 420 | | RR 0.53 | 378 per 1000 | 178 fewer 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 UFH (95% CI) |
| asymptomatic) | (4 studies)<br>14 days | MODERATE[a]<br>due to risk of bias | (0.38 to 0.73) | | (from 102 fewer to 234 fewer) |
| PE | 290<br>(3 studies)<br>time-point not reported | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | RR 1.16<br>(0.4 to 3.38) | 35 per 1000 | 6 more per 1000<br>(from 21 fewer to 83 more) |
| Fatal PE | 130<br>(1 study)<br>time-point not reported | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | Peto OR 1<br>(0.06 to 16.16) | 15 per 1000 | 0 fewer per 1000<br>(from 14 fewer to 186 more) |
| Wound infection | 150<br>(2 studies)<br>time-point not reported | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | RR 0.9<br>(0.39 to 2.08) | 133 per 1000 | 13 fewer per 1000<br>(from 81 fewer to 144 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 17: Clinical evidence summary: UFH + AES (length unspecified) 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 (length unspecified) | Risk difference with UFH + AES (length unspecified) (95% CI) |
| All-cause mortality | 52<br>(1 study)<br>time-point not reported | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | Peto OR 0.1<br>(0.01 to 0.97) | 130 per 1000 | 116 fewer per 1000<br>(from 3 fewer to 129 fewer) |
| DVT (symptomatic and | 52<br>(1 study) | VERY LOW[a,c] | RR 0.99 | 348 per 1000 | 3 fewer per 1000 |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with AES (length unspecified) | Risk difference with UFH + AES (length unspecified) (95% CI) |
| asymptomatic) | 10 days | due to risk of bias, imprecision | (0.47 to 2.1) | | (from 184 fewer to 383 more) |
| PE | 52 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 1.59 (0.15 to 16.42) | 43 per 1000 | 26 more per 1000 (from 37 fewer to 670 more) |
| Major bleeding | 52 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 70 fewer to 70 more)[d] |
| Fatal PE | 52 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Peto OR 0.1 (0 to 5.39) | 43 per 1000 | 39 fewer per 1000 (from 43 fewer to 153 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.
d Absolute effects could not be calculated due to zero events in the control arm

**Table 18: Clinical evidence summary: VKA 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 VKA (95% CI) |
| All-cause mortality | 436 (3 studies) 90 days | LOW[a,b] due to risk of bias, imprecision | RR 0.75 (0.52 to 1.08) | 239 per 1000 | 60 fewer per 1000 (from 114 fewer to 19 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 VKA (95% CI) |
| DVT (symptomatic and asymptomatic) | 424 (3 studies) 10 days | MODERATE[a] due to risk of bias | RR 0.47 (0.34 to 0.64) | 351 per 1000 | 186 fewer per 1000 (from 126 fewer to 231 fewer) |
| PE | 360 (2 studies) 90 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Peto OR 0.51 (0.1 to 2.55) | 22 per 1000 | 11 fewer per 1000 (from 20 fewer to 33 more) |
| Major bleeding | 236 (2 studies) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 1.73 (0.88 to 3.37) | 93 per 1000 | 68 more per 1000 (from 11 fewer to 221 more) |
| Fatal PE | 200 (1 study) 90 days | LOW[a,b] due to risk of bias, imprecision | RR 0.14 (0.02 to 1.14) | 70 per 1000 | 60 fewer per 1000 (from 69 fewer to 10 more) |
| Deep wound infection | 76 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 0.75 (0.18 to 3.13) | 105 per 1000 | 26 fewer per 1000 (from 86 fewer to 224 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 if the outcome definition reported did not meet definition of outcome in protocol

**Table 19: Clinical evidence summary: Aspirin (± other prophylaxis) versus no aspirin (± other prophylaxis)**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with No aspirin | Risk difference with Aspirin (95% CI) |
| All-cause mortality | 13356 | | RR 0.97 | 69 per 1000 | 2 fewer per 1000 |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with No aspirin | Risk difference with Aspirin (95% CI) |
| | (1 study)<br>35 days | MODERATE[b]<br>due to indirectness | (0.85 to 1.1) | | (from 10 fewer to 7 more) |
| PE | 13356<br>(1 study)<br>35 days | LOW[a,b]<br>due to imprecision and indirectness | RR 0.74<br>(0.45 to 1.2) | 6 per 1000 | 1 fewer per 1000<br>(from 3 fewer to 1 more) |
| Fatal PE | 13356<br>(1 study)<br>35 days | MODERATE[b]<br>due to indirectness | RR 0.42<br>(0.24 to 0.72) | 6 per 1000 | 4 fewer per 1000<br>(from 2 fewer to 5 fewer) |
| Wound infection | 13356<br>(1 study)<br>35 days | LOW[a,b]<br>due to imprecision and indirectness | RR 1.17<br>(0.87 to 1.56) | 13 per 1000 | 2 more per 1000<br>(from 2 fewer to 7 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 outcome definition reported did not meet definition of outcome in protocol

**Table 20: Clinical evidence summary: IPCD (thigh-length) 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 IPCD (95% CI) |
| DVT (symptomatic and asymptomatic) | 304<br>(1 study)<br>14 days | MODERATE[a]<br>due to risk of bias | Peto OR 0.14<br>(0.04 to 0.53) | 57 per 1000 | 48 fewer per 1000<br>(from 26 fewer to 54 fewer) |
| PE | 304<br>(1 study)<br>5-10 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.37<br>(0.07 to 1.78) | 38 per 1000 | 24 fewer per 1000<br>(from 35 fewer to 29 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

| 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 IPCD (95% CI) |
| risk of bias<br>b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. | | | | | |

## 25.4 Economic evidence

**Published literature**

Two economic models were developed for this population in CG92 with the relevant comparison and have been included in this review.[224] These are summarised in the health economic evidence profiles below (**Table 21** and Table 22) and the health economic evidence tables in appendix J.

Two economic studies relating to this review question were identified but were excluded due to limited applicability or methodological limitations.[47,80] These are listed in appendix O, with reasons for exclusion given.

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

**Table 21: Health economic evidence profile: pharmacological, mechanical or combination of prophylaxis strategies vs each other**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| NCGC 2010 [CG92][224] [UK] | Partially applicable [(a)] | Potentially serious limitations [(b)] | **Study design**: Decision analytic model<br>**Population**:<br>Adults admitted for hip fracture surgery in England.<br>**Interventions:**<br>1. Fondaparinux sodium (2.5 mg subcutaneously)<br>2.Warfarin variable dose (adjusted to INR range 2 to 3, average dose 4mg/day)<br>3. LMWH (average of dalteparin 5000 units subcutaneous daily) and enoxaparin (4000 units subcutaneous daily)<br>4. UFH (5000 units three times daily)<br>5. IPCD-FID<br>6.Aspirin (High dose)<br>7. No prophylaxis | NR | NR | **Incremental net monetary benefit (INMB)** (pa)<br>1. **Fondaparinux sodium:** £2148 (rank 1)<br>2. **Warfarin variable dose**: £1830 (rank 2)<br>3. **LMWH**: 1711 (rank 3)<br>4. **UFH**: £1465 (rank 4)<br>5. **IPCD-FID:** £999 (rank 5)<br>6. **Aspirin (high dose):** £558 (rank 6)<br>7. **No prophylaxis:** £0 (rank 7) | For patients with a very low bleeding risk fondaparinux was the most cost-effective strategy, with a probability of 85% of being the most cost-effective strategy. LMWH tended to be more cost-effective as the risk of major bleeding increased. |

*Abbreviations: FID: foot impulse device; ICER: incremental cost-effectiveness ratio; IPCD: intermittent pneumatic compression; LMWH : low molecular weight heparin; NR: not reported; pa: probabilistic analysis*

*(a) Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context. Some of the interventions are not included in the current clinical review, for example: aspirin (high dose), warfarin (variable dose) and UFH.*

*(b) The relative treatment effect applied to all VTE events in the model is the relative treatment effect obtained from the DVT NMA.*

**Table 22: Health economic evidence profile: fondaparinux (post-discharge) vs no post-discharge prophylaxis**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| NCGC 2010 [CG92][224] ([UK]) | Directly applicable [(a)] | Potentially serious limitations [(b)] | **Study design**: Decision analytic model<br>**Interventions:**<br>1. No post discharge prophylaxis (it is not clear whether prophylaxis was given during the initial hospital stay)<br>2. Post-discharge prophylaxis with fondaparinux for 10 days | NR | NR | **Incremental net monetary benefit (INMB)** (pa)<br>1. **No prophylaxis**: £0 (rank 2)<br>2. **Fondaparinux**: £239 (rank 1) | Fondaparinux had 92% probability of being the cost-effective strategy at £20K threshold.<br><br>In a threshold analysis, post-discharge fondaparinux was no longer cost-effective if greater than 55% of patients require district nurse visits to deliver their prophylaxis. |

*Abbreviations: BNF: British National Formulary; 95% CI: 95% confidence interval; INMB: incremental net monetary benefit; NR: not reported; pa: probabilistic analysis.*

*(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 MA.*

## 25.5 Evidence statements

**Clinical**

**Pharmacological and mechanical interventions versus no VTE prophylaxis**

Four of the comparisons compared interventions with no VTE prophylaxis, three were pharmacologically based comparisons. For the comparison of LMWH versus no prophylaxis, data presented suggested possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic) and PE and possible clinical harm in terms of all-cause mortality and wound infection, although there was uncertainty associated with all of these results. There was no clinical difference in terms of major bleeding. Quality of the evidence for this comparison ranged from very low to low due to risk of bias, imprecision and indirectness. For the comparison of UFH versus no prophylaxis, there was no clinical difference between UFH and no prophylaxis for the outcomes of PE, fatal PE and wound infection. However the large uncertainty in these results means they could also be consistent with both benefit and harm. Clinical benefit of UFH was reported in terms of DVT and possible clinical harm in terms of all-cause mortality, although the mortality outcome could also have been consistent with no difference when taking uncertainty into account. Quality of the evidence for this comparison ranged from very low to moderate due to risk of bias, imprecision and indirectness. Vitamin K antagonist (VKA) compared with no prophylaxis presented clinical benefit of DVT (symptomatic and asymptomatic) without any imprecision. There was a possible clinical benefit due to imprecision in terms of the outcomes all-cause mortality, PE and fatal PE. There was however, possible clinical harm of VKA in terms of major bleeding and no clinical difference in regards to deep wound infection. Quality of the evidence for this comparison ranged from very low to moderate due to risk of bias, imprecision and indirectness.

Lastly, for data reported for the mechanical intervention of IPCD versus no prophylaxis, there was a possible clinical benefit of IPCD in terms of PE, although there was imprecision around this result and clinical benefit of IPCD in terms of DVT (symptomatic and asymptomatic). Quality of the evidence for this comparison ranged from very low to moderate due to risk of bias and imprecision.

**LMWH at a standard dose for a standard duration versus other pharmacological interventions**

When compared with UFH, LMWH has a possible clinical benefit in terms of all-cause mortality, although the imprecision around this result was also consistent with no difference or harm. Moderate quality evidence showed clinical harm in terms of PE. Quality of evidence for this comparison ranged from very low to moderate due to risk of bias, indirectness and imprecision. Compared with fondaparinux, there was no clinical difference in terms of all-cause mortality, PE, major bleeding, and fatal PE, however very serious imprecision around these results presents considerable uncertainty. Moderate quality, precise evidence showed clinical harm in terms of DVT (symptomatic and asymptomatic). Quality of evidence for this comparison ranged from very low to moderate due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration followed by rivaroxaban compared with rivaroxaban, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and fatal PE were reported in one study. There was possible clinical harm of LMWH followed by rivaroxaban in terms of all-cause mortality, DVT (symptomatic and asymptomatic), PE and fatal PE. However there was very serious imprecision around these effect estimates. The quality of the evidence ranged from very low to low due to imprecision and indirectness.

LMWH at a standard dose for a standard duration followed by rivaroxaban was compared with LMWH at a standard dose for an extended duration, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and fatal PE were reported in one study. There was possible

clinical benefit of LMWH followed by rivaroxaban in terms of DVT (symptomatic and asymptomatic) and PE. However the uncertainty around these results was also associated with no difference or clinical harm. There was no clinical difference in terms of all-cause mortality and fatal PE, although again there was considerable uncertainty around these results too. The quality of the evidence was very low due to imprecision and indirectness.

**LMWH at a standard dose for an extended duration versus rivaroxaban**

LMWH at a standard dose for an extended duration compared with rivaroxaban, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and fatal PE were reported in one study. There was possible clinical harm of LMWH followed by rivaroxaban in terms of all-cause mortality, DVT (symptomatic and asymptomatic), PE and fatal PE. However there was considerable uncertainty around all these results. The quality of the evidence was very low due to imprecision and indirectness.

**Fondaparinux (extended duration) versus fondaparinux (standard duration)**

There was a reported clinical benefit of fondaparinux for an extended duration when compared to fondaparinux for a standard duration. There was a possible clinical benefit in terms of PE and fatal PE, although these results were uncertain. Moderate quality, precise evidence showed clinical benefit in terms of DVT (symptomatic and asymptomatic). There was no clinical difference between the two durations of fondaparinux in terms of all-cause mortality and there was possible clinical harm of an extended duration of fondaparinux in terms of major bleeding, however this finding was also consistent with no difference when taking uncertainty into account. Quality of evidence for this comparison ranged from low to moderate due to risk of bias and imprecision.

**Aspirin (± other prophylaxis) versus no aspirin (± other prophylaxis)**

There was a clinical benefit of aspirin in terms of all-cause mortality and fatal PE. There was a possible clinical benefit for PE although this finding was uncertain and could also have been consistent with no difference. There was no clinical difference between aspirin and no aspirin in terms of wound infection, however the uncertainty around this result could also have been consistent with a harm with aspirin. Quality of evidence for this comparison ranged from low to moderate due to indirectness and imprecision.

**Combination comparison: UFH + AES versus AES alone**

In this comparison, unfractionated heparin used with AES had possible clinical benefit over AES alone in terms of all-cause mortality and fatal PE. Contrastingly, there was possible clinical harm of UFH used with AES in terms of PE. There was no clinical difference between the two interventions in terms of DVT (symptomatic and asymptomatic) and major bleeding. However results for all outcomes had uncertainty. Quality of evidence for this comparison was all very low due to risk of bias, indirectness and imprecision.

**Economic**

- One cost-utility analysis found that the following interventions were cost-effective (having positive incremental net monetary benefit [INMB]) compared to no prophylaxis in patients with fragility fractures of the hip: fondaparinux sodium (INMB: £2,148), warfarin variable dose (INMB: £1,830), low molecular weight heparin (INMB: £1,711), unfractionated heparin (INMB: £1,465), intermittent pneumatic compression-foot impulse devices (INMB: £999) and aspirin (high dose; INMB: £558). This analysis was assessed as partially applicable with potentially serious limitations.

- One cost–utility analysis found that, in people with fragility fractures of the hip, fondaparinux (post-discharge) was cost effective (INMB: £239) compared to no post-discharge prophylaxis . This analysis was assessed as directly applicable with potentially serious limitations.

## 25.6 Recommendations and link to evidence

| | |
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| **Recommendations** | **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:**<br>• **LMWH[d], starting 6–12 hours after surgery or**<br>• **fondaparinux sodium[e], starting 6 hours after surgery, providing there is low risk of bleeding. [2018]**<br><br>**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[f] or 24 hours before surgery for fondaparinux sodium[g]. [2018]**<br><br>**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]** |
| **Research recommendation** | **7. 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?**<br><br>**8. What is the clinical and cost effectiveness of IPCD in combination with pharmacological prophylaxis strategies for people with fragility fractures of the pelvis, hip or proximal femur?** |
| 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), fatal PE (7-90 days from hospital discharge), and major bleeding (up to 45 days from |

[d] 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.

[e] 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.

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), 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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| | hospital discharge) as critical outcomes.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) and infection (duration of study) as important outcomes.<br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Fifteen studies were included in this review; thirteen of the relevant studies were randomised controlled trials identified from the previous guideline (CG92). One new study was identified and one study published before CG92 is now included in this review. One of the previously included studies in this evidence review was excluded and moved to the major trauma review due to more appropriate applicability of the study population.<br>Nine comparisons were included; they evaluated both pharmacological and mechanical interventions. Pharmacological interventions included LMWH at standard dose and for a standard duration, UFH, fondaparinux (standard duration and extended duration), VKA and aspirin. Mechanical interventions included AES (length unspecified) and IPCD (thigh-length).<br>Discussion around the quality of the evidence centred largely on the inclusion of the PEP trial which was excluded from the previous guideline. The PEP trial is one of the larger trials conducted in this population that was published in 2000, evaluating the use of aspirin. The committee noted that the PEP trial allowed centres to include other prophylaxis. The data reported include just over 50% of patients with either LMWH or UFH, and around 30% using AES. It is not reported how many of these patients received both heparin and AES, or who had aspirin alone or no prophylaxis at all. The study also reported a post-hoc analysis for the combined outcome of pulmonary embolism and symptomatic DVT. This showed a reduction in symptomatic VTE events using aspirin (plus or minus AES) without the use of heparin and a reduction of symptomatic VTE events with AES (plus or minus the use of heparin). The outcomes of major bleeding or clinically relevant non-major bleeding were not adequately reported in the study and were therefore excluded from the current review. Overall, it was decided that the trial could be included on the basis of providing effectiveness information for the VTE outcomes for aspirin when combined with other prophylaxis, but not for aspirin alone, and that its effect on bleeding was still unknown. |
| Trade-off between clinical benefits and harms | ***Pharmacological and mechanical interventions versus no VTE prophylaxis***<br>The committee discussed the need for prophylaxis in this population and appreciated that in a majority of the evidence where pharmacological or mechanical prophylaxis was compared with no prophylaxis, there were better outcomes in the group receiving an intervention. The committee noted that people with fragility fractures of the pelvis, hip and proximal femur tend to have a longer length of hospital stay; around 21 days for acute spells and 23 for super-spells (may include hospitals differential capture of rehabilitation length-of-stay).[227] Patients have reduced mobility whilst in hospital, a factor that contributes to risk of VTE.<br>General consensus was that IPCD seemed effective as the clinical evidence presented showed clinical benefit for DVT (symptomatic and asymptomatic) and a possible clinical benefit for PE, although there was uncertainty associated with the PE result. The orthopaedic subgroup advised the committee that some hospitals use IPCD routinely in orthopaedic theatres and wards. The use of pharmacological interventions alongside IPCD is common practice but appreciated that there is an absence of RCT evidence evaluating the clinical effectiveness of this combination intervention in this population. It was therefore suggested that a research recommendation be proposed in order to encourage this evaluation. |

Some members of the subgroup were of the view that the use of IPCD may discourage mobilisation. Therefore the subgroup and committee agreed to recommend IPCD only when pharmacological prophylaxis was contraindicated and only until people are able to mobilise themselves. Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a patient is mobile.

***LMWH at a standard dose for a standard duration versus other pharmacological interventions***

The committee considered that the evidence sufficiently supports the use of LMWH and fondaparinux. It was discussed that UFH is not commonly used in current practice. It was previously recommend for patients with renal failure, but low doses of LMWH are currently used in practice instead for these patients.

The committee discussed the evidence presented for LMWH versus fondaparinux and noted that the clinical evidence suggests a higher clinical benefit of fondaparinux over LMWH, as seen in moderate quality evidence for a clinically important reduction in the rate of DVT with fondaparinux compared to LMWH. The committee considered other aspects of the interventions that were not listed as outcomes in the review, such as the half-life of each, with regard to considering situations where prophylaxis would need to be reversed. Fondaparinux has a half-life of 17 hours whereas LMWH has a much shorter half-life ranging from 2–5 hours depending on which preparation is used (according to summary of product characteristics). The committee decided to also recommend LMWH based on the effectiveness evidence showing a possible benefit when compared with no prophylaxis for DVT and PE, although there was uncertainty around these effect estimates. Recommending LMWH is in line with current practice as it is already widely used in this population and is not associated with a high bleeding risk, as is the case with fondaparinux. The committee discussed the major bleeding risk associated with fondaparinux and suggested that it only be used once haemostasis has been established and there is no risk of bleeding. The committee discussed the duration of prophylaxis and noted that the duration of VTE prophylaxis identified in the studies ranged between 28-31 days. The committee acknowledged that recommending VTE prophylaxis for a month is more pragmatic. The committee noted the increased benefit of an extended duration of fondaparinux as reported in one of the studies included in this evidence review.

***Aspirin (± other prophylaxis) versus no aspirin (± other prophylaxis)***

The PEP trial was discussed at length. The committee were aware that some of the orthopaedic community believe aspirin is an appropriate form of prophylaxis, and that the PEP trial provides evidence for its use in this population. The committee were also aware that aspirin is recommended in the American College of Clinical Pharmacy (ACCP) as a method of VTE prophylaxis in this population. The orthopaedic subgroup considered the evidence showed that aspirin alone is an effective method of prophylaxis and advised it should be recommended for this population. However, the committee was concerned about the lack of evidence for aspirin alone particularly around bleeding that is commonly associated with the use of aspirin. Therefore they did not consider that it should be recommended in this population. A research recommendation was proposed to investigate the effectiveness and safety of aspirin compared with the other routinely used pharmacological prophylaxis – LMWH, in people with fragility fractures of the pelvis, hip or proximal femur.

***Combination comparison: UFH + AES versus AES alone***

The committee noted that combination prophylaxis has limited benefit so suggested that the CG92 recommendation which recommends combined prophylaxis should not be adopted unless mobility is reduced. The committee expressed concerns about the overuse of AES in current practice within this population with little evidence of clinical benefit. It was also noted that AES are difficult to fit, applying them can be

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| | painful to the patient and they are not always worn properly. Therefore, it was agreed that the use of AES should not be specified in the recommendation. Although the committee believe that AES should not be routinely used they noted that they may be effective for patients with a high risk of bleeding. |
| Trade-off between net clinical effects and costs | Two economic models were developed for this population in CG92 and were included in this review. The first model compared all standard duration prophylaxis strategies. This analysis showed that fondaparinux (2.5 mg) was the most cost-effective strategy, with an incremental net monetary benefit (INMB) of £2,148. This analysis was assessed as partially applicable, with potentially serious limitations.<br><br>The second model compared fondaparinux initiated post-operatively and continued for 10 days to no post-discharge prophylaxis. This analysis showed that fondaparinux was cost effective compared to no prophylaxis, with an INMB of £239. This analysis was assessed as directly applicable with potentially serious limitations.<br><br>Additionally, two studies were identified but were selectively excluded due to the availability of the more applicable models from CG92.<br><br>The committee discussed the relevance of the clinical evidence used in the CG92 model to the evidence included in the current review. It was acknowledged that there were differences between the interventions included in the model and those included in the current clinical review, where aspirin (high dose) is not used in clinical practice in the UK.<br><br>The committee also highlighted that there was no evidence to support the use of AES for lower limb fragility fractures and that they are difficult to fit, necessitating time from the nurses to ensure they are properly fitted and monitored. Hence, it was concluded that the routine use of AES in this population represents a financial burden on the NHS without evidence of cost effectiveness. The committee discussed the evidence available for the use of IPCD and concluded that this is the only mechanical prophylaxis method that has clinical and cost-effectiveness evidence to support its use in the early post-operative period until mobilisation. It was acknowledged that although there might be an upfront cost of providing IPCDs in hospitals, this is likely to be offset by the saving achieved from not using AES and the standardisation of practice. It was also highlighted that, in most cases, IPCDs are provided rent-free to hospitals and the only cost involved would be that of the sleeves. Additionally, IPCDs are used for a shorter period of time until mobilisation.<br><br>The committee discussed the evidence for pharmacological prophylaxis in this population and noted that the CG92 model showed the cost effectiveness of LMWH (standard dose) and fondaparinux compared to no prophylaxis. Based on the clinical evidence in this update and the trade-off between clinical benefits and harms, the committee decided to retain the CG92 recommendation of these options, giving clinicians the ability to choose between them based on clinical and individual factors.<br><br>The orthopaedic subgroup discussed the evidence for aspirin, all of which came from the PEP trial and considered its lower cost compared to LMWH and fondaparinux. They concluded that it is very likely to be a cost-effective option in this population. However, the committee considered the PEP trial to show evidence of clinical effectiveness of aspirin as an add-on prophylaxis option rather than stand-alone, and its cost effectiveness should be considered in this context. Hence, the committee determined that the pharmacological options that could be recommended should be limited to LMWH and fondaparinux. However, the committee acknowledged the potential value for money that could be achieved if aspirin is proven to be effective as a stand-alone prophylaxis strategy. Hence, the committee made a research recommendation to assess the clinical and cost effectiveness of aspirin in this population. |
| Other considerations | There are 70,000 hip fractures a year in England, Wales and Northern Ireland (National Hip Fracture Database; http://www.nhfd.co.uk/). This population is associated with older and frail people, with the mean age of patients being 82 years |

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| | (http://www.nhfd.co.uk/). Age is a significant risk factor for VTE and bleeding, thus it is important that prophylaxis is provided for these patients. There is an increasing trend to mobilise patients post-operation from day 0 in this population, which can reduce the risk of VTE.<br>There was a lengthy discussion about the lack of evidence evaluating DOACs in this review population. DOACs are currently licensed in the orthopaedic populations of elective hip replacement surgery and elective knee replacement surgery. The subgroup understood that the absence of evidence about these interventions in this review population prohibited a suggested recommendation but appreciated that there may be some clinical benefit and cost saving from these interventions.<br>The committee made a high-priority research recommendation on aspirin alone, and a research recommendation on IPCD, in this population group; see appendix R for more details. |

# 26 Elective hip replacement surgery

## 26.1 Introduction

Elective total hip replacement may be associated with a higher risk of VTE compared with other surgical populations. The population covered in this section of the guideline are those patients undergoing elective hip replacement surgery for any indication. Emergency hip replacement surgery following fracture of the proximal femur is covered in chapter 25.

One objection to using pharmacological VTE prophylaxis is the increased risk of bleeding as a result of anticoagulation. The benefit of VTE prophylaxis has to be weighed against the risks and consequences of a post-operative bleed.

This guideline aims to provide guidance on the appropriate prophylaxis against VTE and its sequelae following elective hip replacement.

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

For full details see review protocol in appendix C.

**Table 23: PICO characteristics of review question**

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| **Population** | Adults and young people (16 years and older) undergoing elective hip replacement admitted to and discharged from hospital |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to |

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| | maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (2.5mg twice daily)<br>• Dabigatran (220mg once daily; 150mg once daily - patients with moderate renal impairment, interacting medicines, over 75 years old)<br>• Rivaroxaban (10mg once daily)<br>• Aspirin (up to 300mg)*<br><br>*off-label |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br>• Surgical site haematoma (up to 45 days from hospital discharge)<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) |

| | |
|---|---|
| | • Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Infection (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

## 26.3 Clinical evidence

Fifty studies were included in the review, these are summarised in Table 24 below. Forty-one studies were previously included in the previous guideline (CG92); [12 14 23 62,63,66 67 84 83,97,99 100 105,106 108 130,145 147 161 163 181 182 183 195 200 201 240 242 243 244 247 262 264 266,270 289 298 299 307 309,328 59 221] and nine studies were added in the update; [157 65 86 87 8 132 187 326 31]

Two technology appraisals were previously included in the previous guideline; [228 229]. One of the technology appraisals [229]; evaluated evidence from studies that were identified in the update [86,157]. Three systematic reviews that were previously included in CG92 have been included in this update; [7,146,167] these are summarised below in Table 24.

Twenty-eight studies that were previously included in CG92 have been excluded: [3 27,270 71,72 96 101 110 124 133 134,135 140 148 184 196 205 221 258 267 274 277 283 288 304 314 323,327], reasons for exclusion include incorrect intervention, no relevant extractable outcomes and incorrect population. One study was previously included in CG92, within the hip fracture evidence review [59], this has been included in this evidence review as the population is more appropriate.

Two Cochrane reviews [98 261] were identified which looked at low-molecular-weight heparin, unfractionated heparin and vitamin-K antagonists for the prevention of venous thromboembolism people undergoing elective hip replacement. The reviews included studies which were included in the previous guideline (CG92) and in the update.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 25, Table 26, Table 27, Table 28, Table 29, Table 30, Table 31, Table 32, Table 33, Table 34, Table 35, Table 36, Table 37, Table 38, Table 39, Table 40, Table 41, Table 42, Table 43, Table 44, Table 45, Table 46, Table 47, Table 48,Table 49, Table 50, Table 51, Table 52, Table 53, Table 54, Table 55, Table 56, Table 57, Table 58, Table 59, Table 60, Table 61, Table 62, Table 63, Table 64, Table 65, Table 66, Table 67, Table 68, Table 69, Table 70, Table 71, Table 72, Table 73, Table 74, Table 75, Table 76, Table 77). 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.

In order to input the clinical effectiveness data of multiple possible interventions into the economic model, it was proposed that a network meta-analysis be carried out on the outcome data for DVT, PE and major bleeding. For full details on the NMA methodology and results, please see appendix M.

**Table 24: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Anderson 2013 [8] | Intervention (n=400):<br>LMWH, extended duration, dalteparin, 5000 IU once daily (standard dose), subcutaneously given from the morning after surgery for 10 days. | n=785<br><br>People undergoing elective total hip replacement, mean duration of | All-cause mortality (90 days)<br><br>PE (90 days): confirmed by compression ultrasonography (definition unclear) | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Continued course of dalteparin (combined with placebo aspirin tablets) for 28 more days<br><br>Comparison (n=385):<br>LMWH, dalteparin, 5000 IU once daily (standard dose), subcutaneously given from the morning after surgery for 10 days followed by Aspirin, 81 mg orally for 28 more days | surgery 92 minutes<br><br>Age (mean): 57.8 years<br>Gender (male to female ratio): 1.3:1<br><br>Multicentre, Canada | Fatal PE (90 days)<br><br>Major bleeding (90 days): defined as fatal bleeding, symptomatic bleeding into a critical area or organ, or bleeding that caused 20g/L decrease or more in haemoglobin level or led to transfusion of 2 or more units of whole blood or red blood cells.<br><br>Clinically relevant non-major bleeding: resulted in hospitalisation, reoperation, aspiration, or a wound hematoma complicated by infection.<br><br>Heparin-induced thrombocytopaenia (90 days)<br><br>Wound infection (90 days) | |
| Avikainen 1995 [12] | Intervention (n=83):<br>LMWH, enoxaparin, 40mg (standard dose), subcutaneously given preoperatively and repeated daily for 10 days.<br><br>Comparison (n=84):<br>Unfractionated heparin, 5000IU. Begun 2 hours before the operation and repeated twice daily for 10 days | n=167<br><br>People undergoing elective hip replacement surgery, mean duration of surgery not reported<br><br>Age (mean): 65 years<br>Gender (male to female ratio): 1:2<br><br>Finland | DVT (symptomatic and asymptomatic) (10-14 days): confirmed by ultrasonography<br><br>PE (time-point not clearly reported): confirmed by ventilation–perfusion | Included in CG92 |
| Bailey 1991 [14] | Intervention (n=50):<br>Intermittent pneumatic compression device (IPCD), applied from after surgery in recovery ward until day 7. AES applied on admission until discharge. | n=95<br><br>People undergoing elective total hip replacement, mean duration of surgery 197 minutes | DVT (symptomatic and asymptomatic) (7 days): confirmed by venography or B-mode Doppler ultrasonography and technecium-pyrophosphate red-cell labelled nuclear venogram with impedance plethysmography. | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison (n=45):<br>Warfarin, 10mg evening before surgery (7.5mg for women over 70 and patients with minor abnormalities of liver function tests). Doses given after surgery adjusted to maintain a prothrombin time at 14-16 seconds. Prothrombin times routinely obtained by postoperative day 2 or 3. AES applied on admission until discharge. | Age (mean): 65 years<br>Gender (male to female ratio): 1:1<br><br>USA | Clinically relevant non-major bleeding (7 days): defined as "clinically important bleeding" | |
| Bergqvist 1996B [23] | Intervention (n=131):<br>LMWH, enoxaparin, 40mg (standard dose), subcutaneously administered once daily. First dose was given 12±2 hours preoperatively until day 21.<br><br>Comparison (n=131):<br>Placebo or single dose of 0.4ml saline | n=262<br><br>People undergoing elective total hip replacement surgery, mean duration of surgery was 1.9 hours.<br><br>Age (mean): 70 years<br>Gender (male to female ratio): 1:1.3<br><br>Sweden | DVT (symptomatic and asymptomatic) (90 days): confirmed by bilateral ascending phlebography<br><br>PE (90 days): confirmed by ventilation-perfusion lung scan or a pulmonary angiography | Included in CG92 |
| Bern 2015[31] | Intervention (n=64)<br>Fondaparinux, 2.5mg once daily, orally from 6 or more hours (no later than 6AM the next day) postoperatively, or 6-8 hours after epidural catheter removal, continued for 28±2 days. IPCD was worn for duration on stay in hospital. AES were prescribed for use after discharge. | n=118<br><br>People undergoing elective primary unilateral total knee replacement surgery, mean duration of surgery not reported<br><br>Age (mean): 61 years<br>Gender (male to female ratio): 1:1 | All-cause mortality (30 days)<br><br>DVT (symptomatic and asymptomatic) (30 days): confirmed by bilateral duplex sonography<br><br>PE (30 days): confirmed by ventilation/perfusion lung scan or computerised axial tomography angiogram | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison (n=54)<br>VKA, warfarin, dose of 5.0mg the night before surgery, followed by 5.0mg the evening of surgery, variable dose (target INR 2.0-2.5) until day 28±2 days.<br>IPCD was worn for duration on stay in hospital. AES were prescribed for use after discharge. | USA | | |
| Cohen 2007 [59] | Intervention (n=430):<br>Fondaparinux, 2.5 mg, once daily, subcutaneously given for 5-9 days. First dose of fondaparinux was given six hours after wound closure and the second dose 18-24 hours later. Subsequent doses were administered 22-26 hours. AES, above-knee, applied pre-operatively and worn for 35-49 days.<br><br>Comparison (n=426):<br>Fondaparinux, 2.5 mg, once daily, subcutaneously given for 5-9 days. First dose of fondaparinux was given six hours after wound closure and the second dose 18-24 hours later. Subsequent doses were administered 22-26 hours. | n=856<br><br>People undergoing elective total hip replacement<br><br>Age (mean): 65 years<br>Gender (male to female ratio): 1: 1.33<br><br>Brazil, UK, Hong Kong and Spain | All-cause mortality (35-49 days)<br><br>Major bleeding (35-49 days): defined as fatal bleeds; bleeding which lead to re-operation or into critical organs; clinically-overt bleeding associated with a fall in haemoglobin level of 2 g/dl or to transfusion of two or more units, or warranting cessation of treatment.<br><br>Fatal PE (35-49 days): definition not reported<br><br>Clinically relevant non-major bleeding (35-49 days): defined as non-major bleeding requiring intervention or unscheduled contact, or with patient discomfort<br><br>Health-related quality of life (35-29 days): EQ-5D (medians reported, narratively reported) | Included in CG92 – was in the hip fracture review |
| Colwell 1994A [63] | Intervention 1 (n=203):<br>LMWH, enoxaparin, 40mg once daily (standard dose) subcutaneously administered, within 24 hours after surgery and continued for a | n=610<br><br>People undergoing elective hip replacement surgery, including primary and | All-cause mortality (7 days)<br><br>DVT (symptomatic and asymptomatic) (7 days): confirmed by bilateral contrast venography | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | maximum of 7 days.<br><br>Intervention 2 (n=195)<br>LMWH, enoxaparin, 30mg once daily (high dose), subcutaneously administered, within 24 hours after surgery and continued for a maximum of 7 days.<br><br>Comparison (n=209):<br>Unfractionated heparin, 5000IU, administered every 8 hours, within 24 hours after surgery and continued for a maximum of 7 days | revision procedures, mean duration of surgery not reported<br><br>Age (mean): 65.3 years<br>Gender (male to female ratio): 1:1.04<br><br>Multicentre, USA | PE (7 days): definition not reported<br><br>Major bleeding (7 days): definition not reported | |
| Colwell 1999 [62] | Intervention (n=1516)<br>LMWH, enoxaparin, 30mg twice daily (high dose), every 12 hours subcutaneously given until discharge. Administered within 24 hours postoperatively.<br><br>Comparison (n=1495)<br>Warfarin, started at 7.5mg, adjusted to maintain INR ratio between 2.0 to 3.0. Administered between 48 hours preoperatively and 24 hours postoperatively.<br><br>Concomitant treatment<br>AES permitted, further details not reported | n=3011<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported<br>Age (mean): 64 years<br>Gender (male to female ratio): 1:1.25<br><br>Multicentre, USA | All-cause mortality (90 days)<br><br>PE (90 days): confirmed by ventilation perfusion scan or pulmonary angiography<br><br>Major bleeding (time-point not reported) | Included in CG92<br><br>Significantly more obese patients in the intervention arm |
| Comp 2001 [66] | Intervention (n=224):<br>LMWH, enoxaparin, 30 mg twice daily (high dose) subcutaneously for 7-10 days. Patients were then administered 40mg once daily subcutaneously for 3 weeks (extended duration). | n=435<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported | DVT (symptomatic and asymptomatic) (27-29 days): confirmed by segment-filling defects on lower-extremity ascending contrast venograms.<br><br>PE (27-29 days): confirmed by high-probability ventilation-perfusion lung scan or pulmonary | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | Comparison (n=211):<br>LMWH, enoxaparin, 30 mg twice daily (high dose) subcutaneously for 7-10 days (standard duration). Patients were then administered placebo, saline subcutaneously for 3 weeks. | Age (mean): 64 years<br>Gender (male to female ratio): 1:1<br><br>Multicentre, USA | angiogram<br><br>Major bleeding (27-29 days): defined as clinically overt and resulted in death, transfusion of two or more units of blood products, a decrease in haemoglobin level of ≥2.0 g/dL (≥20 g/L) compared with the most recent preceding postoperative value, or a serious or life-threatening clinical event or one requiring surgical intervention or if it was retroperitoneal, intracranial, or intraocular in location.<br><br>Heparin-induced thrombocytopaenia (27-29 days) | |
| Dahl 1997[67] | Intervention (n=117):<br>LMWH, dalteparin, 5000 IU once daily (standard dose), subcutaneously administered from the evening before the operation until 4 weeks after (extended duration). AES, below-knee on both legs before the operation and for the first post-operative week.<br><br>Comparison (n=110):<br>LMWH, dalteparin, 5000 IU once daily (standard dose), subcutaneously administered from the evening before the operation until 7 days after (standard duration), then administered placebo (sodium chloride) in the evenings. AES, below-knee on both legs before the operation and for the first post-operative | n=227<br><br>People undergoing elective primary or secondary hip replacement, mean duration of surgery 107 minutes<br><br>Age (mean): 71.2 years<br>Gender (male to female ratio): 1:2.4<br><br>Norway | DVT (symptomatic and asymptomatic) (35 days): confirmed by bilateral ascending venography<br><br>PE (35 days): confirmed by ventilation/perfusion scintigraphy (V/Q scan) and chest X-rays | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | week. | | | |
| Eriksson 1991A[84] | Intervention (n=67): LMWH, dalteparin, 5000 IU once daily (standard dose) subcutaneously from the evening before the operation until 10 days post-operation. Placebo was also given twice daily.<br><br>Comparison (n=69): Unfractionated heparin, 5000 IU three times daily, subcutaneously from two hours pre-operation for 10 days. Placebo was only given on the pre-operative evening.<br><br>Concomitant treatment: Mobilisation and physiotherapy started on the first day after the operation | n=132<br><br>People undergoing elective total hip replacement, mean duration of surgery 124 minutes<br><br>Age (mean): 69 years<br>Gender (male to female ratio): 1:1.4<br><br>Sweden | DVT (symptomatic and asymptomatic) (12-14 days): confirmed by bilateral ascending phlebography<br><br>PE (12-14 days): confirmed by pulmonary perfusion scintigraphy<br><br>Major bleeding (10 days): definition not reported<br><br>Heparin-induced thrombocytopaenia (time-point not reported)<br><br>Haematoma > 0.5 cm at site of injection (time-point not reported) | Included in CG92 |
| Eriksson 2007[83] :RENOVATE I study | Intervention (n=1157): Dabigatran etexilate, 220 mg once daily (started 1–4 hours after surgery with a half dose of 110 mg) subcutaneously. Intervention continued for 28-35 days.<br><br>Comparison (n=1174): LMWH, enoxaparin, 40 mg once daily (standard dose) subcutaneously, administered from the evening before the operation for 28-35 days. | n=2319<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported<br><br>Age (mean): 65 years<br>Gender (male to female ratio): 1:1<br><br>Multinational – Europe, Australia and South Africa | DVT (symptomatic and asymptomatic) (28-35 days): confirmed by a consistent intraluminal filling defect on at least two venogram images.<br><br>PE (28-35 days): confirmed by ventilation-perfusion scintigraphy, pulmonary angiography, spiral chest CT, or by autopsy.<br><br>Major bleeding (28-35 days): defined as a bleeding event that meets at least one of the following criteria: fatal bleeding, critical bleeding (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, in a non-operated joint, or intramuscular with | Included in CG92<br>TA157200[8][229] |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | | | compartment syndrome, clinically overt bleeding (at surgical or extra-surgical site) associated with a decrease in the haemoglobin level of more than 2 g/dL (20 g/l; 1.24 mmol/L), clinically overt bleeding (at surgical or extra-surgical site) leading to transfusion of two or more units of whole blood or packed cells, bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (e.g. draining or puncture of an haematoma at the surgical site, transfer to an ICU or emergency room) | |
| Eriksson 2008[86]: RECORD I study | Intervention (n=2266): LMWH, enoxaparin, 40mg once daily (standard dose), subcutaneously given from the evening before the surgery, restarted 6-8 hours after wound closure, continued to day 35 (extended duration). Placebo tablets were given.<br><br>Comparison (n=2275): Rivaroxaban, 10mg, orally administered from 6-8 hours after wound closure until day 35. Placebo injections were given. | n=4541<br><br>People undergoing elective total hip replacement, mean duration of surgery 91 minutes<br><br>Age (mean): 63 years<br>Gender (male to female ratio): 1:1<br><br>Austria, Australia, Argentina, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Lithuania, Netherlands, Norway, Poland, Slovakia, South Africa, Spain, Sweden, Turkey, USA | All-cause mortality (36 days)<br><br>DVT (symptomatic and asymptomatic) (36 days):confirmed by ascending bilateral venography using Rabinov and Paulin technique<br><br>PE (36 days): confirmed by spiral computed tomography, perfusion-ventilation lung scintigraphy or pulmonary angiography<br><br>Major bleeding (37 days): defined as bleeding that was fatal, occurred in a critical organ (e.g. retroperitoneal, intracranial, intraocular, and intraspinal bleeding), or required reoperation or extrasurgical-site bleeding that was clinically overt and was associated with a fall in the haemoglobin level of at least 2 g/dl or that required transfusion of 2 or more units of whole blood or packed cells<br><br>Clinically relevant non-major | New study<br><br>TA1702009 [229] |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | bleeding (37 days): definition not reported<br><br>Wound infection (37 days) | |
| Eriksson 2011[87]: RE-NOVATE II trial | Intervention (n=992):<br>LMWH, enoxaparin, 40 mg (standard dose) and placebo drug, subcutaneously given from the evening before surgery and continued for 28-35 days.<br><br>Comparison (n=1001):<br>Dabigatran, 220mg (110 mg x2) once daily, orally administered from the evening before surgery and continued for 28-35 days. | n=1993<br><br>People undergoing primary, unilateral, elective hip replacement, median duration 80 minutes<br><br>Age (mean): 62 years<br>Gender (male to female ratio): 1:1<br><br>Multicentre in 19 countries; Australia, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Hungary, India, Italy, Netherlands, New Zealand, Norway, Poland, South Africa, Spain, Sweden, USA. | All-cause mortality (38 days)<br><br>DVT (symptomatic and asymptomatic) (36 days): confirmed by ascending, bilateral venography using a modification of the Rabinov and Paulin technique.<br><br>PE (36 days): confirmed by ventilation-perfusion scintigraphy and chest X-ray, pulmonary angiography, spiral chest computer tomography, or by autopsy<br><br>Major bleeding (36 days): defined as a bleeding event that meets at least one of the following criteria: fatal bleeding, critical bleeding (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, in a non-operated joint, or intramuscular with compartment syndrome, clinically overt bleeding (at surgical or extra-surgical site) associated with a decrease in the haemoglobin level of more than 2 g/dL (20 g/l; 1.24 mmol/L), clinically overt bleeding (at surgical or extra-surgical site) leading to transfusion of two or more units of whole blood or packed cells, bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (e.g. draining or puncture of an haematoma at the surgical site, transfer to an ICU or emergency room). [taken from European Medicines Agency guideline] | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | Clinically relevant non-major bleeding (36 days): defined as any clinically overt bleeding that does not meet the criteria for major bleeding but requires medical attention (e.g. hospitalisation, medical treatment for bleeding) and/or change in antithrombotic therapy (including discontinuation or down-titration of study drug) and/or any other bleeding type considered to have clinical consequences for a patient. [taken from European Medicines Agency guideline] | |
| Fordyce 1992 [97] | Intervention (n=39):<br>Foot pump, A-V Impulse System, rapid inflation and deflation for 3 seconds, cycle repeated every 20 seconds. Fitted to the foot of the operated limb, and using whenever the patient was in bed or sitting at rest. Duration of intervention unclear. AES was also applied to both legs<br><br>Comparison (n=40):<br>AES on both legs alone. Duration of intervention unclear.<br><br>Concomitant treatment:<br>Patients practiced active leg exercise and were mobilised on the 2nd postoperative day | n=79<br><br>People undergoing elective primary total hip replacement, mean duration of surgery 109 minutes.<br><br>Age (mean): 70 years<br>Gender (male to female ratio): 1:1.7<br><br>UK | DVT (symptomatic and asymptomatic) (6-9 days): confirmed by ascending venography | Included in CG92 |
| Francis 1992[99] | Intervention (n=98):<br>Intermittent pneumatic compression device (IPCD), bilateral thigh- | n= 291<br><br>People undergoing elective hip | DVT (symptomatic and asymptomatic) (6-8 days): confirmed by venography | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | calf, 35-55 mmHg. Bilateral thigh-high AES. Applied immediately prior to surgery. Continued until outcome assessment at 6-8 days.<br><br>Comparison (n=103):<br>Warfarin, low dose adjusted to achieve INR of 1.5 on day of surgery, and 2.5 post-operatively. Bilateral thigh-high AES. Applied immediately prior to surgery. Continued until outcome assessment at 6-8 days.<br><br>Concomitant treatment:<br>Patients moved from bed to chair on 2nd day post-operation, began ambulation and physical therapy on 3rd day post-operation. | replacement, mean duration of surgery not reported.<br><br>Age (mean): 64 years<br>Gender (male to female ratio): 1:1.12<br><br>USA | | |
| Francis 1997A[100] | Intervention (n=271):<br>LMWH, dalteparin, 5000IU once daily (standard dose) subcutaneously for mean of 7 days from the first postoperative day. First dose of 2500IU was administered two hours before the operation; second dose of 25000IU was given on the evening of the operation.<br><br>Comparison (n=279):<br>Warfarin, adjusted to an INR of approximately 2.5, orally. First dose administered evening before the operation and second dose | n=550<br><br>People undergoing elective primary of revision total hip replacement, mean duration of surgery not reported<br><br>Age (mean): 63 years<br>Gender (male to female ratio): 1:1<br><br>USA | DVT (symptomatic and asymptomatic) (9 days): confirmed by bilateral ascending venography<br><br>Major bleeding (9 days): defined as fatal or if the patient required a transfusion, a reoperation or prolonged hospital stay<br><br>Wound haematoma (9 days) | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | administered evening of the day of the operation. Dose for first and second dose: 5-7.5 mg, (depending on weight: 5mg for patients that weighed ≤57 kg; 7.5 for patients that weighed >57kg). | | | |
| Fuji 2008[105] | Intervention (n=81): Fondaparinux, 2.5mg subcutaneously once daily. Administered 24±2 hours after surgery until 10-16 days. More than 50% received AES.<br><br>Comparison (n=82): Placebo, 0.25ml isotonic sodium chloride, subcutaneously once daily. Administered 24±2 hours after surgery until 10-16 days. More than 50% received AES. | n=163<br><br>People undergoing primary elective total hip replacement or revision surgery, mean duration of surgery not reported<br><br>Age (mean): 61.6 years<br>Gender (male to female ratio):4.6:1<br><br>Japan | All-cause mortality (11-17 days)<br><br>Major bleeding (11-17 days): defined as fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with bleeding index of 2 or more. | Included in CG92 |
| Fuji 2008A[106] | Intervention 1 (n=81): LMWH, enoxaparin, 20mg (low dose), subcutaneously once daily, administered 24-36 hours after surgery for 14 days. More than 50% received AES (length unspecified).<br><br>Intervention 2 (n=80): LMWH, enoxaparin, 40mg (standard dose) once daily, administered 24-36 hours after surgery for 14 days. More than 50% received AES (length unspecified).<br><br>Comparison (n=86): Placebo (saline). Administered 24-36 hours after surgery for | n=247<br><br>People undergoing primary elective hip replacement, mean duration of surgery not reported<br><br>Age (mean): 62 years<br>Gender (male to female ratio): 1:8<br><br>Japan | DVT (symptomatic and asymptomatic) (14 days): confirmed by Doppler ultrasound<br><br>PE (90 days): confirmed by ventilation perfusion lung scans or pulmonary angiography<br><br>Major bleeding (15 days): defined as bleeding episode that was retroperitoneal, intracranial, or intraocular or if it was associated with: death; transfusion of ≥2 units of packed red blood cells or whole blood (except autologous); a reduction of ≥2 g/d; or a serious or life threatening clinical events that required medical intervention. | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | 14 days. More than 50% received AES (length unspecified). | | | |
| Gallus 1983[108] | Intervention (n=43): Intermittent pneumatic compression device (IPCD), calf compression, 45 mmHg for 10 seconds each 2 minutes. Device was applied to both legs throughout surgery then day and night for 7 days.<br><br>Comparison (n=47): Control group, no further details reported | n=90<br><br>People undergoing elective hip replacement, mean duration of surgery not reported<br><br>Age (mean): 68 years<br>Gender (male to female): 1:2<br><br>Australia | DVT (symptomatic and asymptomatic) (7 days): confirmed by 125I fibrinogen leg scan or venography | Included in CG92 |
| Hampson 1974[130] | Intervention (n=48): Unfractionated heparin (calcium heparin), 5000 I subcutaneously three times daily for 7-10 days after surgery<br><br>Comparison (n=52): Control group, saline, subcutaneously three times daily. | n=100<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported<br><br>Age (mean): details not reported<br>Gender (male to female ratio): details not reported<br><br>UK | DVT (symptomatic and asymptomatic) (18 days): confirmed by 125I fibrinogen uptake test and ultrasound investigations<br><br>Major bleeding (time-point not reported): definition not reported | Included in CG92 |
| Hardwick 2011[132] ; Colwell 2010[65] | Intervention (n=194): LMWH, enoxaparin, 30 mg twice daily (high dose) subcutaneously from the morning after surgery until discharge. Mean length of stay 3.2 days. LMWH, enoxaparin, 40 mg once daily (standard dose) until 10 days post-operation. | n=392<br><br>People undergoing elective primary unilateral total hip replacement, mean duration of surgery 94 minutes<br><br>Age (mean): 63 years | DVT (symptomatic and asymptomatic): (84 days) confirmed by bilateral duplex ultrasonography<br><br>PE (84 days):confirmed by spiral computed tomographic scans<br><br>Major bleeding (10 days): definition not reported | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | Comparison (n=198):<br>IPCD, on both of the patient's calves, 50 mmHg for 8 seconds followed by 36-45 seconds of decompression. IPCD applied in the operating room and continued use for 10 days after surgery. | Gender (male to female): 1:1<br><br>USA | | |
| Hull 1990[147] | Intervention (n=152):<br>IPCD, calf and thigh length, 50-65 mmHg, was applied postoperatively in the recovery room until hospital discharge or for 14 days<br><br>Comparison (n=158):<br>Control group, no prophylaxis, no further details reported<br><br>Concomitant treatment<br>Routine physiotherapy provided to all patients | n=310<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported.<br><br>Age (mean): 65 years<br>Gender (male to female ratio): 1:1.5<br><br>Canada | DVT (symptomatic and asymptomatic) (14 days): confirmed by bilateral ascending venography<br><br>PE (14 days): confirmed by ventilation-perfusion lung scanning and pulmonary angiography | Included in CG92 |
| Hull 2000 [145] | Intervention 1 (n=496):<br>LMWH, dalteparin, 2500IU (low dose) subcutaneously 2 hours before surgery (pre-operatively), a second dose of 2500IU postoperatively. Patients also received placebo oral capsules.<br><br>Intervention 2 (n=487):<br>LMWH, dalteparin, 2500IU (low dose) subcutaneously postoperatively, placebo administered before the operation. Patients also received placebo oral capsules.<br><br>Comparison (n=489): | n=1472<br><br>People undergoing elective unilateral total hip replacement, mean duration of surgery not reported<br><br>Age (mean): 64 years<br>Gender (male to female ratio): 1:1.08<br><br>USA and Canada | All-cause mortality (8 days)<br><br>DVT (symptomatic and asymptomatic) (8 days): confirmed by venography<br><br>PE (8 days): confirmed by lung scanning or pulmonary angiography<br><br>Major bleeding (8 days): defined as clinically overt and associated with a decrease in haemoglobin level of 20 g/L or more or required transfusion of 2 U of blood or more; if it was intracranial, intraocular, intraspinal or retroperitoneal; or if it occurred into a prosthetic joint | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | Warfarin, initial dose of 10mg postoperatively in the evening of surgery day. Doses were adjusted daily to maintain an INR from 2.0 to 3.0. Patients also received subcutaneous placebo injections<br><br>Concomitant treatment:<br>AES used in approximately 30% in intervention groups | | Wound haematoma (8 days) | |
| Kakkar 2000[161] | Intervention (n=149):<br>LMWH, bemiparin, 35000IU (high dose) plus placebo injections of 0.9% saline subcutaneously, administered 2 hours before surgery and continued for at least 8 days post-operation (longer if person was still hospitalised)<br><br>Comparison (n=149):<br>Unfractionated heparin (calcium heparin), 5000IU subcutaneously, administered 2 hours before surgery and continued for at least 8 days post-operation (longer if person was still institutionalised) | n=298<br><br>People undergoing elective hip replacement surgery, mean duration of surgery 105 minutes<br><br>Age (mean): 70.5 years<br>Gender (male to female ratio): 1:2<br><br>UK | DVT (symptomatic and asymptomatic) (28 days): confirmed by bilateral elective venography<br><br>PE (28 days): confirmed by ventilation perfusion scan.<br><br>Fatal PE (28 days): confirmed by ventilation perfusion scan.<br><br>Wound haematoma (28 days) | Included in CG92 |
| Kakkar 2008[157]: RECORD II study | Intervention (n=1257):<br>LMWH, enoxaparin, 40 mg once daily (standard dose) subcutaneously, administered from 12 hours before surgery, restarted 6-8 hours (with placebo tablets for 31-39 days) after wound closure and continued for 10-14 days (standard | n=2509<br><br>People undergoing elective total hip replacement, mean duration of surgery 94 minutes.<br><br>Age (mean):61.6 years<br>Gender (male to | All-cause mortality (30-42 days)<br><br>DVT (symptomatic and asymptomatic) (32-40 days): confirmed by venography<br><br>PE (32-40 days): confirmed by pulmonary angiography, perfusion/ventilation lung scintigraphy with chest radiography, or spiral computed tomography. | New study.<br><br>TA1702009[229] |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | duration).<br><br>Comparison (n=1252):<br>Rivaroxaban, 10mg once daily, orally administered 6-8 hours after wound closure (with placebo injections for 10-14 days), continued for 31-39 days | female): 1:1<br><br>Multicentre; 123 centres across 21 countries (details of countries not reported) | Major bleeding (30-42 days): defined as bleeding that was fatal, was into a critical organ (retroperitoneal, intracranial, intraocular, intraspinal), required re-operation, or clinically overt extra surgical site bleeding associated with a fall in haemoglobin of 20 g/L or more, calculated from the day 1 post-operative baseline value, or requiring infusion of two or more units of whole blood or packed cells.<br><br>Clinically relevant non-major bleeding (30-42 days): definition not reported.<br><br>Wound infection (30-42 days) | |
| Kalodiki 1996[163] | Intervention 1 (n=32):<br>LMWH, enoxaparin, 40 mg, once daily subcutaneously for 8-12 days<br><br>Intervention 2 (n=32):<br>LMWH, enoxaparin, 40mg, once daily (standard dose) subcutaneously and AES for 8-12 days<br><br>Comparison (n=14):<br>Control group, placebo injections once daily subcutaneously | n=78<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported<br><br>Age (mean): details not reported<br>Gender (male to female ratio): 1:1<br><br>USA | DVT (symptomatic and asymptomatic) (8-12 days): confirmed by bilateral ascending venography<br><br>PE (8-12 days): confirmed by perfusion/ventilation scan | Included in CG92 |
| Lassen 1991[183] | Intervention (n=93):<br>LMWH, tinzaparin, 50 IU/kg, once daily (low dose) subcutaneously, from 2 hours preoperatively and continued for 7 days. AES, thigh-length, both legs, from one hour before the operation | n=190<br><br>People undergoing elective hip replacement, mean duration of surgery 120 minutes | DVT (symptomatic and asymptomatic) (8-10 days): confirmed by bilateral ascending phlebography<br><br>PE (8-10 days): confirmed by ventilation/perfusion lung scintimetry | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | until 7 days post-operation.<br><br>Comparison (n=97):<br>Placebo group, saline once daily subcutaneously. AES, thigh-length, both legs, from one hour before the operation until 7 days post-operation. | Age (mean):67 years<br>Gender (male to female ratio): 1:1<br><br>Denmark | Fatal PE (8-10 days): confirmed by ventilation/perfusion lung scintimetry | |
| Lassen 1998[182] | Intervention (n=140):<br>LMWH, dalteparin, 5000 IU once daily (standard dose) subcutaneously, from 12 hours before operation until 35 days after operation (extended duration).<br><br>Comparison (n=141):<br>LMWH, dalteparin, 5000 IU once daily (standard dose) subcutaneously, from 12 hours before operation until 7 days post-operation (standard duration). Placebo, isotonic sodium chloride subcutaneously administered until 35 days<br><br>Concomitant treatment:<br>AES permitted, no further details reported | n=281<br><br>People undergoing elective total hip replacement, mean duration of surgery 108 minutes<br><br>Age (mean): 69 years<br>Gender (male to female ratio): 1:1.3<br><br>Denmark | DVT (symptomatic and asymptomatic) (35 days): confirmed by ultrasonography or phlebography<br><br>PE (35 days): confirmed by perfusion/ventilation lung scan or pulmonary angiography<br><br>Major bleeding (35 days): definition not reported | Included in CG92 |
| Lassen 2002[181] | Intervention (n=1154):<br>LMWH, enoxaparin, 40 mg (standard dose) once daily and placebo subcutaneously, administered from 12±2 hours preoperatively until day 5 to 9. Use of AES was recommended, 71% used AES. | n=2309<br><br>People undergoing primary elective total hip-replacement surgery or revision surgery, mean duration of surgery 2.4 hours | All-cause mortality (49 days)<br><br>DVT (symptomatic and asymptomatic) (49 days): confirmed by systematic bilateral ascending venography<br><br>PE (49 days): confirmed by lung scan, pulmonary angiography or helical computed tomography or at | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | Comparison (n=1155):<br>Fondaparinux sodium, 2.5mg and placebo subcutaneously, administered 6±2 hours postoperatively until day 5 to 9. Use of AES was recommended, 71% used AES.<br><br>Concomitant treatment:<br>Use of NSAIDs or aspirin intervention group 54%, comparison group 53% | Age (mean): 67 years<br>Gender (male to female ratio): 1:1.23<br><br>Country not reported | autopsy<br><br>Major bleeding (49 days): defined as fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with bleeding index of 2 or more. | |
| Lassen 2010[187]: ADVANCE-3 trial | Intervention (n=2699):<br>LMWH, enoxaparin, 40mg once daily (standard dose) subcutaneously, administered 12 hours before surgery until after surgery (duration of intervention not clearly reported), plus placebo tablets twice daily<br><br>Comparison (n=2708):<br>Apixaban, 2.5mg orally twice daily plus placebo injections once daily, from 12 to 24 hours after closure of the surgical wound until after surgery (duration of intervention not clearly reported) | n=5407<br><br>People undergoing elective total hip replacement or revision of a previously inserted hip prosthesis, mean duration of surgery 90 minutes<br><br>Age (mean): 61 years<br>Gender (male to female ratio): 1:1<br><br>Denmark | All-cause mortality (32-38 days)<br><br>DVT (symptomatic and asymptomatic) (32-38 days): confirmed by bilateral venography<br><br>PE (32-38 days): confirmed by bilateral venography<br><br>Major bleeding (32-38 days): defined as acute, clinically overt bleeding accompanied by one or more of the following findings: a decrease in the haemoglobin level of 2g/dl or more over a 24 hour period; transfusion of 2 or more units of packed red cells; bleeding at a critical site (including intracranial, intraspinal, intraocular, pericardial, and retroperitoneal bleeding); bleeding into the operated joint, necessitating reoperation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding.<br><br>Fatal PE (32-38 days)<br><br>Clinically relevant non-major | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | | | bleeding (32-38 days): acute, clinically overt episodes such as wound haematoma, bruising, or ecchymosis, gastrointestinal bleeding, haemotypsis, haematuria, or epistaxis that did not met the criteria for major bleeding<br><br>Heparin-induced thrombocytopaenia (32-38 days) | |
| Levine 1991[195] | Intervention (n=332):<br>LMWH, enoxaparin, 30mg twice daily (high dose) subcutaneously, from 12-24 hours after surgery continued for 14 days or until discharge if sooner.<br><br>Comparison (n=333):<br>Unfractionated heparin, 7500IU twice daily subcutaneously, from 12-24 hours after surgery continued for 14 days or until discharge if sooner. | n=665<br><br>People undergoing elective hip replacement, mean duration of surgery not reported.<br><br>Age (mean): details not reported<br>Gender (male to female ratio): details not reported<br><br>Country not reported | DVT (symptomatic and asymptomatic) (10-14 days): confirmed by 125I fibrinogen leg scanning, impedance plethysmography and venography<br><br>PE (10-14 days): definition not reported<br><br>Major bleeding (10-14 days): definition not reported | Included in CG92 |
| Manganelli 1998[200] | Intervention (n=33):<br>Unfractionated heparin, 5000IU, from one day pre-operation, every 8 hours for 30 days (extended duration).<br><br>Comparison (n=28):<br>Unfractionated heparin, 5000IU, from one day pre-operation every 8 hours until discharge (standard duration). Length of stay (mean): 12 days | n=61<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported<br><br>Age (mean): 66 years<br>Gender (male to female ratio): 1:1.5<br><br>Italy | DVT (symptomatic and asymptomatic) (45 days): confirmed by unilateral ascending venography<br><br>Major bleeding (45 days): defined as clinically overt and associated with a decrease in haemoglobin values of 2 g/dl or more, compared with the last post-op value, or a need for blood transfusion, or if it was retroperitoneal or intracranial. | Included in CG92 |
| Mannucci | Trial 1 | Trial 1: n=96 | Trial 1 | Included in |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| 1976[201] | Intervention (n=45):<br>Unfractionated heparin (calcium heparin), 5000 IU subcutaneously, from 2 hours preoperatively and 8 hourly postoperatively until fully ambulatory on crutches.<br><br>Comparison (n=51):<br>Control group, no further details reported<br><br>Trial 2<br>Intervention (n=23):<br>Unfractionated heparin (calcium heparin), 5000 IU subcutaneously, from 2 hours preoperatively and 8 hourly postoperatively until fully ambulatory on crutches.<br>(Intervention not explicitly detailed, assumption that details are the same as trial 1)<br><br>Comparison (n=24):<br>Control group, no further details reported | Trial 2: n=47<br><br>People undergoing elective hip replacement, mean duration of surgery for trial 1: 117 minutes, trial 2: 121 minutes<br><br>Trial 1 and 2<br>Age (mean): 60 years<br>Gender (male to female): 1:4<br>(Reported that age and gender is similar in both trials)<br><br>Italy | DVT (symptomatic and asymptomatic) (7 days): confirmed by 125I fibrinogen test<br><br>PE (time-point not reported): definition not reported<br><br>Wound haematomas (time-point not reported)<br><br>Trial 2<br>DVT (symptomatic and asymptomatic) (15 days): confirmed by 125I fibrinogen test<br><br>PE (time-point not reported): definition not reported<br><br>Wound haematomas (time-point not reported) | CG92<br><br>Data from both trials were combined in analysis |
| Moskovitz 1978[221] | Intervention (n=35):<br>Unfractionated heparin, sodium heparin, 5000IU subcutaneously given every 8 hours. Patients wore AES (length unspecified), length of time AES worn for not reported.<br><br>Comparison (n=32):<br>Placebo, saline, subcutaneously given | n=67<br><br>People admitted for elective hip replacement surgery, mean duration of surgery not reported<br><br>Age: 46% ≥60 years; 54% <59 years<br>Gender (male to | All-cause mortality (time-point not reported)<br><br>DVT (symptomatic and asymptomatic) (10 days): confirmed by $I^{125}$ fibrinogen uptake test and scans<br><br>PE (time-point not reported): confirmed by radionuclide perfusion lung-scanning<br><br>Major bleeding (time-point | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | every 8 hours. Patients wore AES (length unspecified), length of time AES worn for not reported. | female ratio): 1:1<br><br>USA | not reported): definition not reported | |
| Paiement 1987[240] | Intervention (n=66):<br>Intermittent pneumatic compression device (IPCD, 45-55 mmHg, started one day before operation<br><br>Comparison (n=72):<br>Warfarin, low dose, 10 mg pre-operation, 5 mg post-operation, thereafter adjusted to maintain PTT at 15 seconds for control at 11-12 seconds | n=138<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported<br><br>Age (mean): not reported<br>Gender (male to female ratio):1:1<br><br>Canada | DVT (symptomatic and asymptomatic) (10 days): confirmed by venography<br><br>PE (10 days): was not routinely screened for – confirmed by V/Q and angiogram if high probability<br><br>Major bleeding (10 days): defined as overt and associated with decrease in haemoglobin level if ≥2 g/dl; required transfusion of 2 or more units; retroperitoneal or occurred in major prosthetic joint, intracranial; intraoperative and post-operative blood loss (weight of sponges; suction drainage blood loss; estimated of blood on wound drapes) | Included in CG92 |
| Pitto 2004[242] | Intervention (n=100):<br>LMWH, nadroparin, dose adjusted to body weight, 0.2 to 0.6 ml (0.1ml = 950IU of anti Xa) (variable dose). Mean BMI: 28.1 ± 2.9. Subcutaneously administered every 12 hours postoperatively, not stated when stopped but could be until discharge. Bilateral thigh-high AES also used.<br><br>Comparison (n=100):<br>Foot pump, A-V Impulse System (slippers), patient in Trendelenburg position (head-high, feet-low), 130 mmHg for one second every 20 seconds. Started post- | n=200<br><br>People with osteoarthritis undergoing elective total hip replacement, mean duration of surgery not reported<br><br>Age (mean): 57.7 years<br>Gender (male to female ratio): 1:2<br><br>New Zealand | DVT (symptomatic and asymptomatic) (45 days): confirmed by serial bilateral duplex<br><br>PE (45 days): definition not reported<br><br>Fatal PE (45 days): definition not reported<br><br>Major bleeding (45 days): definition not reported<br><br>Heparin-induced thrombocytopaenia (45 days) | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | operation, not stated when stopped could be used until discharge. Bilateral thigh-high AES also used.<br><br>Concomitant treatment:<br>Physiotherapy and mobilisation with partial weight bearing usually started on postoperative day 2. | | | |
| Planès 1990A[244] | Trial 1<br>Intervention (n=50):<br>LMWH, enoxaparin, 40 mg once daily (standard dose) subcutaneously from 12 hours pre-operation. Duration of intervention unclear, possibly until discharge.<br><br>Comparison (n=50):<br>LMWH, enoxaparin, 60 mg once daily (high dose) subcutaneously from 12 hours pre-operation. Duration of intervention unclear, possibly until discharge.<br><br>Trial 2<br>Intervention (n=124):<br>LMWH, enoxaparin, 40mg once daily (standard dose), subcutaneously from 12 hours pre-operatively for 14 days or until hospital discharge.<br><br>Comparison (n=113):<br>Unfractionated heparin (calcium heparin), 5000 IU, subcutaneously every 8 hours from 2 hours pre-operation for 14 | Trial 1: n=100<br>Trial 2: n=237<br><br>People undergoing elective hip replacement, mean duration of surgery not reported<br><br>Trial 1<br>Age (mean): 65 years<br>Gender (male to female ratio):1:1<br><br>Trial 2<br>Age (mean): not reported<br>Gender (male to female ratio): not reported<br><br>Both trials conducted in France | Trial 1<br>DVT (symptomatic and asymptomatic) (12-15 days): confirmed by bilateral ascending venography<br><br>Wound haematomas (12-15 days)<br><br>Trial 2<br>DVT (symptomatic and asymptomatic) (time-point unclear): confirmed by bilateral ascending venography<br><br>PE (time-point unclear): definition not reported<br><br>Major bleeding (time-point unclear): definition not reported) | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | days or until hospital discharge. | | | |
| Planes 1996[243] | Intervention (n=90):<br>LMWH, enoxaparin, 40mg once daily (standard dose), subcutaneously from 12 hours pre-operatively, 12 hours postoperatively, until 21±2 days (extended duration)<br><br>Comparison (n=89):<br>Placebo, isotonic saline, 0.4 ml<br><br>Concomitant treatment:<br>Patients were advised to wear elastic bandages/AES on both legs (% of patients that used AES not reported), avoid other anticoagulant treatment, aspirin, ticlopidine and NSAIDS | n=179<br><br>People undergoing elective total hip replacement surgery, mean duration of surgery not reported<br><br>Age (mean): 69 years<br>Gender (male to female ratio): 1.3:1<br><br>France | All-cause mortality (21±2 days)<br><br>DVT (symptomatic and asymptomatic) (21±2 days): confirmed by bilateral phlebographic examination.<br><br>PE (21±2 days): confirmed by pulmonary angiography or by autopsy<br><br>Major bleeding (21±2 days): defined as overt and associated with either a fall in haemoglobin level of ≥20 g/L or a need for transfusion of 2 or more units of blood, or if it was retroperitoneal or intracranial.<br><br>Wound haematoma (21±2 days) | Included in CG92 |
| Prandoni 2002[247] | Intervention (n=184):<br>Warfarin – extended duration, sodium warfarin, 5 mg once daily, starting on the second preoperative day, after the intervention the dosage was adjusted to increase the INR between 2.0 and 3.0. Continued intervention more 4 weeks post-discharge (extended duration).<br><br>Comparison (n=176):<br>Warfarin - standard duration, sodium warfarin, 5 mg once daily, starting on the second preoperative day, after the | n=360<br><br>People undergoing elective hip replacement, duration of study not reported<br><br>Age (mean): 69 years<br>Gender (male to female ratio): 1:1.2<br><br>Italy | All-cause mortality (28 days)<br><br>DVT (symptomatic and asymptomatic) (28 days): confirmed by compression ultrasound or intraluminal filling defect on ascending phlebography<br><br>PE (28 days): confirmed by a high-probability ventilation-perfusion lung scan, a spiral computed tomographic scan, or an abnormal finding on angiography or (in case of death) autopsy.<br><br>Major bleeding (28 days): defined as clinically overt and associated with either a decrease in haemoglobin of at least 2.9 g/dL or a need for a transfusion of 2 of | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | intervention the dosage was adjusted to increase the INR between 2.0 and 3.0. Intervention stopped at discharge | | more units of red blood cells, was intracranial or retroperitoneal or resulted in the permanent discontinuation of anticoagulation. | |
| Samama 1997[262] | Intervention (n=85): LMWH, enoxaparin, 40 mg once daily (standard dose) subcutaneously, administered for 10±2 days<br><br>Comparison (n=85): Placebo, sodium chloride saline for 10±2 days | n=170<br><br>People undergoing elective total hip replacement, mean duration of surgery 70 minutes<br><br>Age (mean): 67.2 years<br>Gender (male to female ratio): 1.4:1<br><br>France | All-cause mortality (90 days)<br><br>DVT (symptomatic and asymptomatic)(12 days): confirmed by ultrasonography or venography<br><br>PE (90 days): confirmed by ventilation-perfusion lung scan or angiography<br><br>Major bleeding (12 days): defined as overt and associated with either a decrease in haemoglobin of 2 g/dl or more, a need for transfusion of 2 nits of more of packed red blood cells, if it was retroperitoneal or intracranial, or if it led to surgical re-intervention or death.<br><br>Wound haematomas (12 days) | Included in CG92 |
| Samama 2002[264] | Intervention (n=644): LMWH, reviparin, 4200IU once daily (high dose) subcutaneously, initial dose 12 hours preoperatively for 3±1 days, continued for 6 weeks (extended duration).<br><br>Comparison (n=645): LMWH, reviparin, initial dose of 4200IU (high dose), 12 hours preoperatively, crossed over to acenocoumarol for 6 weeks after surgery (extended duration). The dose | n=1289<br><br>People undergoing elective unilateral primary total hip replacement, mean duration of surgery not reported<br><br>Age (mean): 66 years<br>Gender (male to female): 1:1<br><br>France | All-cause mortality (42-63 days)<br><br>DVT (symptomatic and asymptomatic) (42-63 days): confirmed by venography or duplex scanning<br><br>PE (42-63 days): confirmed by ventilation-perfusion scanning or angiography<br><br>Major bleeding (42 -63 days): defined as clinically overt and met any of the following criteria: associated with a decrease in the haemoglobin level of more | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | was adjusted to achieve an INR between 2.0 and 3.0 for 2 consecutive days. | | than 20 g/L compared with the pre-randomisation level; it required the transfusion of 2 units of more of packed red blood cells after randomisation; it was digestive, intracranial, retroperitoneal or intraocular; it was located at the surgical site and required a reoperation | |
| Santori 1994[266] | Intervention (n=67):<br>Foot pump, intermittent plantar, on both feet immediately after the operation and used for 7-10 days. Foot pump only used when patients were in bed. AES on both legs, no further information about the length or duration.<br><br>Comparison (n=65):<br>Unfractionated heparin (calcium heparin), 5000IU three times daily for 10 days starting the day before the operation. AES on both legs, no further information about the length of duration.<br><br>Concomitant treatment:<br>Physiotherapy with mobilisation started on the 2nd postoperative day. Walking began on 4th or 5th postoperative day | n=132<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported<br><br>Age (mean): 71.1 years<br>Gender (male to female ratio): 1:2.5<br><br>Italy | DVT (symptomatic and asymptomatic) (42 days): confirmed by thermography and Doppler ultrasonography followed by phlebography | Included in CG92 |
| Tørholm 1991[289] | Intervention (n=58):<br>LMWH, dalteparin, 2500 IU, subcutaneously for the first two doses (2 hours before surgery and 12 hours postoperatively), then | n=112<br><br>People undergoing elective hip replacement, mean duration of surgery 125 | All-cause mortality (time-point not reported)<br><br>DVT (symptomatic and asymptomatic) (9 days): confirmed by 125I fibrinogen test and ascending phlebography | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | 5000 IU subcutaneously for the following six days<br><br>Comparison (n=54):<br>Placebo, sodium chloride 9 g/l subcutaneously using same regimen as intervention group | minutes<br><br>Age (mean): 66 years<br>Gender (male to female ratio): 1:1.24<br><br>Denmark | PE (time-point not reported): definition not reported<br><br>Wound infection (time-point not reported) | |
| Turpie 1986[298] | Intervention (n=50):<br>LMWH, enoxaparin, 30 mg twice daily (high dose) subcutaneously, from 12 to 24 hours after surgery for 14 days or until discharge.<br><br>Comparison (n=50):<br>Placebo, 0.3 ml saline, subcutaneously from 12 to 24 hours after surgery for 14 days | n=100<br><br>People undergoing elective hip replacement, mean duration of surgery 126 minutes<br><br>Age (mean): 67 years<br>Gender (male to female ratio): 1:1<br><br>Canada | All-cause mortality (14 days)<br><br>DVT (symptomatic and asymptomatic) (14 days): venography or 125I fibrinogen scanning<br><br>PE (14 days): definition not clearly reported (venography?)<br><br>Major bleeding (14 days): defined as overt and associate with either a fall in the haemoglobin level of 2 g/dl or more or a need for transfusion of two or more units of blood, or if it was retroperitoneal or intracranial. | Included in CG92 |
| Turpie 2002[299] | Intervention (n=1138):<br>LMWH, enoxaparin (high dose), 30mg twice daily subcutaneously, administered 4-8 hours post-operation, then 12 or more hours afterwards. Treatment was scheduled to continue unto day 5-9. AES used in 85% of patients.<br><br>Comparison (n=1137):<br>Fondaparinux sodium, 2.5mg and a placebo subcutaneously, administered 4-8 hours post-operation, then 12 or more hours afterwards. Treatment | n=2275<br><br>People undergoing primary elective total hip replacement surgery or revision surgery, mean duration of surgery 2.42 hours<br><br>Age (mean): 67 years<br>Gender (male to female ratio): 1:1<br><br>Canada | All-cause mortality (49 days)<br><br>DVT (symptomatic and asymptomatic) (49 days): confirmed by systematic bilateral ascending venography<br><br>PE (49 days): confirmed by systematic bilateral ascending venography<br><br>Fatal PE (49 days): no definition reported<br><br>Major bleeding (49 days): defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved Any other critical | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | was scheduled to continue unto day 5-9. AES used in 86% of patients.<br><br>Concomitant treatment:<br>Physiotherapy was recommended. Anticoagulant/antiplatelet therapy was permitted; mean use 1.6%. NSAIDs or aspirin also permitted; mean use 14% | | organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more | |
| Warwick 1995A[307] | Intervention (n=78):<br>LMWH, enoxaparin, 40mg once daily (standard dose) subcutaneously, administered from 12 hours before operation, then at 12 hours and 36 hours postoperatively. AES, bilateral thigh-length also used<br><br>Comparison (n=78):<br>AES, bilateral thigh-length alone<br><br>Concomitant treatment:<br>All patients were mobilised on the second postoperative day | n=156<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported<br><br>Age (mean): no further details reported<br>Gender (male to female ratio): no further details reported<br><br>UK | DVT (symptomatic and asymptomatic) (8-10 days): confirmed by ipsilateral venography<br><br>PE (8-10 days): confirmed by ventilation/perfusion scan | Included in CG92 |
| Warwick 1998[309] | Intervention (n=143):<br>LMWH, enoxaparin, 40mg (standard dose), once daily subcutaneously for 7 days.<br><br>Comparison (n=147):<br>Foot pump, A-V impulse system, for 7 days, not further details reported. | n=290<br><br>People undergoing elective total hip replacement, mean duration of surgery not reported<br><br>Age (mean): 68 years<br>Gender (male to female ratio): | DVT (symptomatic and asymptomatic) (6-8 days): confirmed by venography<br><br>PE (90 days): confirmed by ventilation perfusion scanning | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | 1.8:1<br><br>UK | | |
| Yokote 2011[326] | Intervention 1 (n=86):<br>LMWH, enoxaparin, 40mg, (20mg twice daily) (standard dose), subcutaneously post-operation for 10 days. AES, thigh-length and IPCD was applied in the operating theatre before the procedure until post-operative day 2.<br><br>Intervention 2 (n=85):<br>Fondaparinux, 2.5 mg once daily, subcutaneously given post-operation for 10 days. AES, thigh-length and IPCD was applied in the operating theatre before the procedure until post-operative day 2.<br><br>Comparison (n=85):<br>Placebo, isotonic saline, 0.5 ml, subcutaneously given post-operation for 10 days. AES, thigh-length and IPCD was applied in the operating theatre before the procedure until post-operative day 2.<br><br>Concomitant treatment:<br>All began mobilisation exercises under supervision of a physiotherapist within 24 hours after surgery. | n=255<br><br>People undergoing elective primary total hip replacement, mean duration of surgery not reported<br><br>Age (mean): 64 years<br>Gender (male to female): 1:4<br><br>Japan | DVT (symptomatic and asymptomatic) (84 days): confirmed by Duplex ultrasonography<br><br>PE (84 days): confirmed by multi-detector CT scan<br><br>Major bleeding (11 days): defined as retroperitoneal, intracranial or intraocular bleeding, or if it was associated with either death, transfusion or more than two units of packed red blood cells or whole blood (except autologous), a reduction in the level of haemoglobin of > 2g/dl, or a serious life-threatening clinical event requiring medical intervention.<br><br>Haematoma: maximum size > 5 cm (11 days) | New study |
| Zanasi 1988[328] | Intervention (n=19):<br>Unfractionated heparin, 5000IU and placebo subcutaneously, | n=44<br><br>People undergoing elective hip | DVT (7 days): confirmed by fibrinogen uptake test<br><br>PE (7 days): definition not | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | administered one day before surgery and continued until 7 postoperative days.<br><br><u>Comparison (n=25):</u><br>Aspirin, 100mg administered on alternate days, started one day before surgery and continued until 7 postoperative days. | surgery<br><br>Age (mean): 70.8 years<br>Gender (male to female ratio): 1:4 | reported<br><br>Fatal PE (7 days): definition not reported | |

**Table 25: 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 LWMH (standard dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 391 (3 studies) 90 days | LOW[a] due to risk of bias | RR 0.46 (0.33 to 0.63) | 408 per 1000 | 220 fewer per 1000 (from 151 fewer to 273 fewer) |
| PE | 391 (3 studies) 90 days | VERY LOW[a,b,c] due to risk of bias, indirectness | RR 0.15 (0.04 to 0.58) | 43 per 1000 | 37 fewer per 1000 (from 18 fewer to 42 fewer) |
| Major bleeding | 914 (4 studies) 11-12 days | LOW[a] due to risk of bias | Peto OR 5.92 (2.13 to 16.46) | 2 per 1000 | 11 more per 1000 (from 2 more to 33 more) |
| Wound haematoma | 319 (2 studies) 10-12 days | LOW[a,b] due to risk of bias, imprecision | RR 1.65 (1.06 to 2.59) | 133 per 1000 | 86 more per 1000 (from 8 more to 211 more) |
| Wound infection | 112 (1 study) timepoint not reported | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.02 (0.43 to 113.83) | 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 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 Absolute effects could not be calculated due to zero events in the control arm

**Table 26: Clinical evidence summary: LMWH (standard dose; standard duration) versus UFH**

| Outcomes | No of | Quality of the evidence | Relative effect | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | (95% CI) | Risk with UFH | Risk difference with LMWH (standard dose) (95% CI) |
|---|---|---|---|---|---|
| All-cause mortality | 278 (1 study) 7 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.14 (0.01 to 2.25) | 14 per 1000 | 12 fewer per 1000 (from 14 fewer to 17 more) |
| DVT (symptomatic and asymptomatic) | 784 (4 studies) 7-14 days | VERY LOW[a,c,d] due to risk of bias, inconsistency, indirectness | RR 0.74 (0.42 to 1.30) | 199 per 1000 | 52 fewer per 1000 (from 116 fewer to 60 more) |
| PE | 941 (4 studies) 7 days | VERY LOW[a,b,d] due to risk of bias, indirectness, imprecision | Peto OR 0.30 (0.09 to 1.04) | 17 per 1000 | 12 fewer per 1000 (from 16 fewer to 1 more) |
| Major bleeding | 774 (3 studies) 7 days | VERY LOW[a,b,c,d] due to risk of bias, inconsistency, indirectness, imprecision | Peto OR 0.36 (0.16 to 0.82) | 47 per 1000 | 29 fewer per 1000 (from 8 fewer to 39 fewer) |
| Wound haematoma | 135 (1 study) not reported | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.29 (0.06 to 1.35) | 103 per 1000 | 73 fewer per 1000 (from 97 fewer to 36 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 heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.
d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 27: Clinical evidence summary: LMWH (standard dose; standard duration) versus VKA**

| Outcomes | No of | Quality of the evidence | Relative effect | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | (95% CI) | Risk with VKA | Risk difference with LMWH (standard dose) (95% CI) |
|---|---|---|---|---|---|
| DVT (symptomatic and asymptomatic) | 382 (1 study) 9 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.77 (1.16 to 2.69) | 146 per 1000 | 112 more per 1000 (from 23 more to 246 more) |
| Major bleeding | 550 (1 study) 9 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.54 (0.44 to 5.41) | 14 per 1000 | 8 more per 1000 (from 8 fewer to 63 more) |
| Wound haematoma | 550 (1 study) 9 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.77 (1.16 to 2.69) | 7 per 1000 | 6 more per 1000 (from 1 more to 12 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 28: Clinical evidence summary: LMWH (standard dose; standard duration) versus dabigatran**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Dabigatran | Risk difference with LMWH (standard dose) (95% CI) |
| All-cause mortality | 1993 (1 study) 35 days | LOW[b] due to imprecision | Peto OR 7.46 (0.15 to 375.79) | 0 per 1000 | -[a] |
| DVT (symptomatic and asymptomatic) | 3351 (2 studies) 35 days | LOW[b,c] due to risk of bias, imprecision | RR 1.18 (0.92 to 1.51) | 63 per 1000 | 11 more per 1000 (from 5 fewer to 32 more) |
| PE | 3770 (2 studies) 35 days | VERY LOW[b,c] due to risk of bias, imprecision | RR 0.82 (0.25 to 2.69) | 3 per 1000 | 1 fewer per 1000 (from 2 fewer to 5 more) |
| Major bleeding | 4313 (2 studies) 28-35 days | MODERATE[b] due to imprecision | RR 0.73 (0.45 to 1.19) | 17 per 1000 | 5 fewer per 1000 (from 9 fewer to 3 more) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Dabigatran | Risk difference with LMWH (standard dose) (95% CI) |
| Clinically relevant non-major bleeding | 2013 (1 study) 28-35 days | LOW[b] due to imprecision | RR 0.88 (0.48 to 1.58) | 23 per 1000 | 3 fewer per 1000 (from 12 fewer to 13 more) |

a Absolute effects could not be calculated due to zero events in the control arm
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 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 29: 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 (standard dose) (95% CI) |
| All-cause mortality | 5407 (1 study) 32-38 days | LOW[a] due to imprecision | Peto OR 0.37 (0.05 to 2.62) | 1 per 1000 | 1 fewer per 1000 (from 1 fewer to 2 more) |
| DVT (symptomatic and asymptomatic) | 3855 (1 study) 32-38 days | HIGH | RR 3.14 (1.95 to 5.06) | 11 per 1000 | 24 more per 1000 (from 11 more to 46 more) |
| PE | 5407 (1 study) 32-38 days | LOW[a] due to imprecision | RR 1.67 (0.4 to 6.99) | 1 per 1000 | 1 more per 1000 (from 1 fewer to 7 more) |
| Major bleeding | 5332 (1 study) 32-38 days | LOW[a] due to imprecision | RR 0.82 (0.44 to 1.53) | 8 per 1000 | 1 fewer per 1000 (from 5 fewer to 4 more) |
| Fatal PE | 5407 (1 study) 32-38 days | LOW[a] due to imprecision | Peto OR 0.14 (0 to 6.84) | 0 per 1000 | 0 fewer per 1000 (from 0 fewer to 2 more) |
| Clinically relevant non-major | 5332 | MODERATE[a] | RR 1.11 | 41 per | 4 more per 1000 |

| 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 (standard dose) (95% CI) |
| bleeding | (1 study) 32-38 days | due to imprecision | (0.86 to 1.43) | 1000 | (from 6 fewer to 18 more) |
| Heparin-induced thrombocytopaenia | 5332 (1 study) 32-38 days | LOW[a] due to imprecision | RR 1.51 (0.25 to 9.02) | 1 per 1000 | 0 more per 1000 (from 1 fewer to 6 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 30: Clinical evidence summary: LMWH (standard dose; standard duration) versus rivaroxaban**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Rivaroxaban | Risk difference with LMWH (standard duration) (95% CI) |
| All-cause mortality | 1733 (1 study) 30-42 days | MODERATE[a] due to risk of bias | RR 4.74 (2.83 to 7.92) | 20 per 1000 | 74 more per 1000 (from 36 more to 136 more) |
| DVT (symptomatic and asymptomatic) | 1733 (1 study) 30-42 days | MODERATE[a] due to risk of bias | RR 5.04 (2.86 to 8.87) | 16 per 1000 | 65 more per 1000 (from 30 more to 128 more) |
| PE | 1733 (1 study) 30-42 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 3.31 (0.57 to 19.15) | 1 per 1000 | 3 more per 1000 (from 0 fewer to 21 more) |
| Major bleeding | 2509 (1 study) 41 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.82 (0.45 to 1.50) | 18 per 1000 | 3 fewer per 1000 (from 10 fewer to 9 more) |
| Clinically relevant non-major bleeding | 2457 (1 study) 41 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 0.82 (0.52 to 1.3) | 33 per 1000 | 6 fewer per 1000 (from 16 fewer to 10 more) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Rivaroxaban | Risk difference with LMWH (standard duration) (95% CI) |
| Wound infection | 2457<br>(1 study)<br>41 days | LOW[b]<br>due to imprecision | RR 0.75<br>(0.26 to 2.15) | 7 per 1000 | 2 fewer per 1000<br>(from 5 fewer to 7 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 if the outcome definition reported did not meet definition of outcome in protocol

**Table 31: Clinical evidence summary: LMWH (standard dose; standard duration) versus IPCD**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with IPCD | Risk difference with LMWH (standard dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 386<br>(1 study)<br>84 days | LOW[a]<br>due to imprecision | RR 1.03<br>(0.4 to 2.69) | 41 per 1000 | 1 more per 1000<br>(from 24 fewer to 69 more) |
| PE | 390<br>(1 study)<br>84 days | LOW[a]<br>due to imprecision | RR 0.99<br>(0.14 to 6.96) | 10 per 1000 | 0 fewer per 1000<br>(from 9 fewer to 61 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 32: Clinical evidence summary: LMWH (standard dose; standard duration) + AES 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 + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 46<br>(1 study)<br>8-12 days | HIGH | RR 0.27<br>(0.15 to 0.5) | 929 per 1000 | 678 fewer per 1000<br>(from 464 fewer to 789 fewer) |

| 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 + AES (95% CI) |
| PE | 46<br>(1 study)<br>8-12 days | MODERATE[a]<br>due to imprecision | RR 0.17<br>(0.04 to 0.80) | 357 per 1000 | 296 fewer per 1000<br>(from 71 fewer to 343 fewer) |

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

**Table 33: Clinical evidence summary: LMWH (standard dose; standard duration) + 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 LMWH + AES (95% CI) |
| All-cause mortality | 153<br>(1 study)<br>90 days | LOW[b]<br>due to imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000<br>(from 30 fewer to 30 more)[a] |
| DVT (symptomatic and asymptomatic) | 475<br>(3 studies)<br>14 days | VERY LOW[b,c,d]<br>due to risk of bias, inconsistency, imprecision | RR 0.62<br>(0.42 to 0.93) | 406 per 1000 | 154 fewer per 1000<br>(from 28 fewer to 235 fewer) |
| PE | 475<br>(3 studies)<br>90 days | VERY LOW[b,d]<br>due to risk of bias, imprecision | Peto OR 1.02<br>(0.14 to 7.30) | 8 per 1000 | 0 more per 1000<br>(from 7 fewer to 50 more) |

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 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.
d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 34: Clinical evidence summary: LMWH (standard dose) + IPCD + AES versus IPCD + AES**

| Outcomes | No of | Quality of the evidence | Relative effect | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | (95% CI) | Risk with IPCD + AES | Risk difference with LMWH + IPCD + AES (95% CI) |
|---|---|---|---|---|---|
| DVT (symptomatic and asymptomatic) | 166 (1 study) 11 days | LOW[a] due to imprecision | RR 0.83 (0.26 to 2.62) | 72 per 1000 | 12 fewer per 1000 (from 53 fewer to 117 more) |
| PE | 166 (1 study) 11 days | LOW[a] due to imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000 (from 20 fewer to 20 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.<br>b Zero events in both arms. Risk difference calculated in Review Manager. | | | | | |

**Table 35: Clinical evidence summary: LMWH (standard dose; standard duration) + AES 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 LMWH + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 64 (1 study) 8-12 days | LOW[a] due to imprecision | RR 0.67 (0.32 to 1.41) | 375 per 1000 | 124 fewer per 1000 (from 255 fewer to 154 more) |
| PE | 64 (1 study) 8-12 days | LOW[a] due to imprecision | RR 0.67 (0.12 to 3.73) | 94 per 1000 | 31 fewer per 1000 (from 83 fewer to 256 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 36: Clinical evidence summary: LMWH (standard dose; standard duration) versus fondaparinux**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux | Risk difference with LMWH (standard dose) (95% CI) |
| Major bleeding | 2440 (2 studies) 11-49 days | VERY LOW[a,b,c] due to risk of bias, | RR 0.69 (0.44 to 1.07) | 38 per 1000 | 12 fewer per 1000 (from 22 fewer to 3 more) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux | Risk difference with LMWH (standard dose) (95% CI) |
| | | indirectness, imprecision | | | |
| Wound haematoma | 167 (1 study) 11 days | LOW[c] due to imprecision | RR 1.01 (0.21 to 4.87) | 36 per 1000 | 0 more per 1000 (from 28 fewer to 138 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 The majority of the evidence was based on indirect comparisons.
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

**Table 37: Clinical evidence summary: LMWH (standard dose; standard duration) + AES versus fondaparinux + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux + AES | Risk difference with LMWH + AES (95% CI) |
| All-cause mortality | 2273 (1 study) 49 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 2.01 (0.37 to 10.96) | 2 per 1000 | 2 more per 1000 (from 1 fewer to 17 more) |
| DVT (symptomatic and asymptomatic) | 1826 (1 study) 49 days | MODERATE[a] due to risk of bias | RR 2.28 (1.56 to 3.34) | 40 per 1000 | 51 more per 1000 (from 22 more to 93 more) |
| PE | 2252 (1 study) 49 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.01 (0.2 to 4.99) | 3 per 1000 | 0 more per 1000 (from 2 fewer to 10 more) |
| Fatal PE | 2252 (1 study) 49 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.01 (0.06 to 16.08) | 1 per 1000 | 0 fewer per 1000 (from 1 more to 13 more) |
| Major bleeding | 2273 | VERY LOW[a,b,c] | RR 0.69 | 41 per 1000 | 13 fewer per 1000 |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux + AES | Risk difference with LMWH + AES (95% CI) |
| | (1 study)<br>49 days | due to risk of bias, imprecision, indirectness | (0.44 to 1.07) | | (from 23 fewer to 3 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 if the outcome definition reported did not meet definition of outcome in protocol

**Table 38: Clinical evidence summary: LMWH (standard dose) + IPCD + AES versus fondaparinux + IPCD + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux + IPCD + AES | Risk difference with LMWH + IPCD + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 167<br>(1 study)<br>11 days | LOW[a]<br>due to imprecision | RR 0.84<br>(0.27 to 2.66) | 71 per 1000 | 11 fewer per 1000<br>(from 52 fewer to 119 more) |
| PE | 167<br>(1 study)<br>11 days | LOW[a]<br>due to imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000<br>(from 20 fewer to 20 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 39: Clinical evidence summary: LMWH (standard dose; standard duration) versus foot pump**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Foot pump | Risk difference with LMWH (standard dose) (95% CI) |
| DVT (symptomatic and | 274 | VERY LOW[a,b] | RR 0.74 | 176 per 1000 | 46 fewer per 1000 |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Foot pump | Risk difference with LMWH (standard dose) (95% CI) |
| asymptomatic) | (1 study)<br>90 days | due to risk of bias, imprecision | (0.42 to 1.3) | | (from 102 fewer to 53 more) |
| PE | 274<br>(1 study)<br>90 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.13<br>(0 to 6.72) | 7 per 1000 | 6 fewer per 1000<br>(from 7 fewer to 40 more) |
| Fatal PE | 274<br>(1 study)<br>90 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(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 Zero events in both arms. Risk difference calculated in Review Manager.

**Table 40: 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 | 179<br>(1 study)<br>27-29 days | LOW[c]<br>due to imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[a] |
| DVT (symptomatic and asymptomatic) | 678<br>(3 studies)<br>23-35 days | MODERATE[b]<br>due to risk of bias | RR 0.36<br>(0.23 to 0.55) | 207 per 1000 | 133 fewer per 1000<br>(from 93 fewer to 160 fewer) |
| PE | 750<br>(3 studies)<br>23-35 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | Peto OR 0.12<br>(0.00 to 6.19) | 3 per 1000 | 2 fewer per 1000<br>(from 3 fewer to 14 more) |
| Major bleeding | 895<br>(3 studies) | VERY LOW[b,c]<br>due to risk of bias, | Peto OR 0.14 | 2 per 1000 | 2 fewer per 1000 |

| 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) |
| | 23-35 days | imprecision | (0.00 to 6.87) | | (from 2 fewer to 13 more) |
| Heparin-induced thrombocytopaenia | 435<br>(1 study)<br>27-29 days | LOW[c]<br>due to imprecision | RR 1.41<br>(0.24 to 8.37) | 9 per 1000 | 4 more per 1000<br>(from 7 fewer to 70 more) |
| Wound haematoma | 179<br>(1 study)<br>27-29 days | LOW[c]<br>due to imprecision | Peto OR 0.99<br>(0.06 to 15.93) | 11 per 1000 | 0 fewer per 1000<br>(from 11 fewer to 142 more) |

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 41: Clinical evidence summary: LMWH (standard dose; extended duration) + AES versus LMWH (standard dose; standard duration) + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH (standard duration) + AES | Risk difference with LMWH (extended duration) + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 218<br>(1 study)<br>35 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.61<br>(0.38 to 0.97) | 317 per 1000 | 124 fewer per 1000<br>(from 10 fewer to 197 fewer) |
| PE | 217<br>(1 study)<br>35 days | LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.13<br>(0.01 to 1.23) | 28 per 1000 | 25 fewer per 1000<br>(from 28 fewer to 6 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 42: Clinical evidence summary: LMWH (standard dose; extended duration) versus rivaroxaban**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Rivaroxaban | Risk difference with LMWH (extended duration) (95% CI) |
| All-cause mortality | 3153 (1 study) 70 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.14 (0 to 6.98) | 1 per 1000 | 1 fewer per 1000 (from 1 fewer to 4 more) |
| DVT (symptomatic and asymptomatic) | 3153 (1 study) 36 days | MODERATE[a] due to risk of bias | RR 4.52 (2.43 to 8.43) | 8 per 1000 | 26 more per 1000 (from 11 more to 56 more) |
| PE | 3153 (1 study) 36 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.31 (0.05 to 1.78) | 3 per 1000 | 2 fewer per 1000 (from 2 fewer to 2 more) |
| Major bleeding | 4541 (1 study) 36 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.82 (0.52 to 1.30) | 18 per 1000 | 3 fewer per 1000 (from 8 fewer to 5 more) |
| Clinically relevant non-major bleeding | 4433 (1 study) 36 days | LOW[a,b] due to risk of bias, imprecision | RR 0.83 (0.58 to 1.18) | 29 per 1000 | 5 fewer per 1000 (from 12 fewer to 5 more) |
| Wound infection | 4433 (1 study) 36 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.99 (0.37 to 2.64) | 4 per 1000 | 0 fewer per 1000 (from 2 fewer to 6 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 43: Clinical evidence summary: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration) followed by aspirin (extended duration)**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH followed by Aspirin (extended duration) | Risk difference with LMWH (extended duration) (95% CI) |
| All-cause mortality | 785 (1 study) 90 days | LOW[b] due to imprecision | Peto OR 7.12 (0.14 to 358.94) | 0 per 1000 | -[a] |
| PE | 778 (1 study) 90 days | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 7.1 (0.74 to 68.48) | 0 per 1000 | -[a] |
| Fatal PE | 785 (1 study) 90 days | LOW[b] due to imprecision | Not estimable4 | Not estimable[4] | 0 fewer per 1000 (from 0 fewer to 0 more)[d] |
| Major bleeding | 785 (1 study) 90 days | LOW[b] due to imprecision | Peto OR 7.12 (0.14 to 358.94) | 0 per 1000 | -[a] |
| Clinically relevant non-major bleeding | 785 (1 study) 90 days | LOW[b] due to imprecision | Peto OR 1.88 (0.38 to 9.38) | 5 per 1000 | 5 more per 1000 (from 3 fewer to 4 more) |
| Wound infection | 785 (1 study) 90 days | LOW[b] due to imprecision | RR 0.8 (0.35 to 1.83) | 31 per 1000 | 6 fewer per 1000 (from 20 fewer to 26 more) |

a Absolute effect could not be calculated due to zero events in the intervention arm
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 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
d Zero events in both arms. Risk difference calculated in Review Manager.

**Table 44: 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 LWMH (high dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 76 (1 study) 11 days | MODERATE[a] due to risk of bias | RR 0.21 (0.08 to 0.56) | 513 per 1000 | 405 fewer per 1000 (from 226 fewer to 472 fewer) |
| PE | 100 (1 study) 11 days | VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000 (from 40 fewer to 40 more)[b] |
| Major bleeding | 100 (1 study) 11 days | VERY LOW[a,d] due to risk of bias, imprecision | Peto OR 0.51 (0.05 to 4.98) | 40 per 1000 | 19 fewer per 1000 (from 38 fewer to 132 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 Zero events in both arms. Risk difference calculated in Review Manager.
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 45: 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 (high dose) (95% CI) |
| All-cause mortality | 278 (1 study) 7 days | LOW[a,c] due to risk of bias, imprecision | RR 3.65 (0.77 to 17.28) | 14 per 1000 | 37 more per 1000 (from 3 fewer to 229 more) |
| DVT (symptomatic and asymptomatic) | 1016 (3 studies) 10-14 days | VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision | RR 0.57 (0.33 to 0.98) | 203 per 1000 | 87 fewer per 1000 (from 4 fewer to 136 fewer) |
| PE | 1328 | VERY LOW[a,c,d] | Peto OR 0.31 | 10 per | 7 fewer per 1000 |

| 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 (high dose) (95% CI) |
| | (3 studies)<br>10-14 days | due to risk of bias, indirectness, imprecision | (0.05 to 1.81) | 1000 | (from 10 fewer to 8 more) |
| Major bleeding | 1069<br>(2 studies)<br>10-14 days | VERY LOW[a,c,d]<br>due to risk of bias, indirectness, imprecision | RR 0.61<br>(0.35 to 1.06) | 59 per 1000 | 23 fewer per 1000<br>(from 38 fewer to 4 more) |
| Fatal PE | 298<br>(1 study)<br>10-14 days | VERY LOW[a,c]<br>due to risk of bias, imprecision | Peto OR 1.00<br>(0.06 to 16.06) | 7 per 1000 | 0 fewer per 1000<br>(from 6 fewer to 91 more) |
| Wound haematoma | 274<br>(1 study)<br>28 days | VERY LOW[a,c]<br>due to risk of bias, imprecision | RR 1.36<br>(0.51 to 3.65) | 47 per 1000 | 17 more per 1000<br>(from 23 fewer to 124 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 confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 46: Clinical evidence summary: LMWH (high dose; standard duration) versus LMWH (standard dose)**

| 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 | 272<br>(1 study)<br>7 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 7.39<br>(0.15 to 372.38) | 0 per 1000 | -[c] |
| DVT (symptomatic and asymptomatic) | 500<br>(2 studies) | VERY LOW[a,b,d]<br>due to risk of bias, | RR 0.45<br>(0.17 to | 140 per 1000 | 77 fewer per 1000<br>(from 116 fewer to 34 more) |

| 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) |
| | 15 days | imprecision, inconsistency | 1.24) | | |
| PE | 398<br>(1 study)<br>7 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.14 (0 to 7.10) | 5 per 1000 | 4 fewer per 1000<br>(5 fewer to 29 more) |
| Major bleeding | 398<br>(1 study)<br>7 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 2.78<br>(0.75 to 10.31) | 15 per 1000 | 4 fewer per 1000<br>(from 5 fewer to 29 more) |
| Wound haematoma | 100<br>(1 study)<br>15 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 2<br>(0.53 to 7.56) | 60 per 1000 | 60 more per 1000<br>(from 28 fewer to 394 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 Absolute effects could not be calculated due to zero events in the control arm
d Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.

**Table 47: Clinical evidence summary: LMWH (high dose; standard duration) versus fondaparinux**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux | Risk difference with LMWH (high dose) (95% CI) |
| Major bleeding | 2257<br>(1 study)<br>49 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.55<br>(0.26 to 1.14) | 18 per 1000 | 8 fewer per 1000<br>(from 13 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

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux | Risk difference with LMWH (high dose) (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 | | | | | |

**Table 48: Clinical evidence summary: LMWH (high dose) + AES versus fondaparinux + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux + AES | Risk difference with LMWH (high dose) + AES (95% CI) |
| All-cause mortality | 2257 (1 study) 49 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.5 (0.13 to 1.99) | 5 per 1000 | 3 fewer per 1000 (from 5 fewer to 5 more) |
| DVT (symptomatic and asymptomatic) | 1580 (1 study) 49 days | LOW[a,b] due to risk of bias, imprecision | RR 1.46 (1.01 to 2.11) | 56 per 1000 | 26 more per 1000 (from 1 more to 62 more) |
| PE | 2254 (1 study) 49 days | LOW[a,b] due to risk of bias, imprecision | Peto OR 0.13 (0.02 to 0.78) | 4 per 1000 | 4 fewer per 1000 (from 1 fewer to 4 fewer) |
| Fatal PE | 2254 (1 study) 49 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.38 (0.15 to 371.73) | 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<br>b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.<br>c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol<br>d Absolute effects could not be calculated due to zero events in one of the arms | | | | | |

**Table 49: Clinical evidence summary: LMWH (high dose; standard duration) versus VKA**

| Outcomes | No of | Quality of the evidence | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | effect (95% CI) | Risk with VKA | Risk difference with LMWH (high dose) (95% CI) |
|---|---|---|---|---|---|
| All-cause mortality | 3011 (1 study) 43-63 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.89 (0.36 to 2.18) | 7 per 1000 | 1 fewer per 1000 (from 4 fewer to 8 more) |
| PE | 3011 (1 study) 42-63 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.66 (0.23 to 1.84) | 6 per 1000 | 2 fewer per 1000 (from 5 fewer to 5 more) |
| Major bleeding | 3011 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 1.48 (0.42 to 5.23) | 3 per 1000 | 1 more per 1000 (from 2 fewer to 11 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 if the outcome definition reported did not meet definition of outcome in protocol

**Table 50: Clinical evidence summary: LMWH (high dose; extended duration) 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 (high dose; extended duration) (95% CI) |
| All-cause mortality | 1279 (1 study) 42-63 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.13 (0.01 to 2.14) | 3 per 1000 | 3 fewer per 1000 (from 3 fewer to 4 more) |
| DVT (symptomatic and asymptomatic) | 1279 (1 study) 42-63 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.74 (0.38 to 1.44) | 31 per 1000 | 8 fewer per 1000 (from 19 fewer to 14 more) |
| PE | 4280 (2 studies) 90 days | LOW[a,b] due to risk of bias, imprecision | RR 0.48 (0.19 to 1.21) | 6 per 1000 | 3 fewer per 1000 (from 5 fewer to 1 more) |

| 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 (high dose; extended duration) (95% CI) |
| | | | | | |
| Major bleeding | 1279<br>(1 study)<br>42-63 days | LOW[a,c]<br>due to risk of bias, indirectness | RR 0.27<br>(0.13 to 0.53) | 58 per 1000 | 42 fewer per 1000<br>(from 27 fewer to 51 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.
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 51: Clinical evidence summary: LMWH (low dose; pre-operation) 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 (low dose; pre-op) (95% CI) |
| All-cause mortality | 985<br>(1 study)<br>8 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.99<br>(0.14 to 6.97) | 4 per 1000 | 0 fewer per 1000<br>(from 4 fewer to 24 more) |
| DVT (symptomatic and asymptomatic) | 675<br>(1 study)<br>8 days | LOW[a]<br>due to risk of bias | RR 0.45<br>(0.31 to 0.64) | 240 per 1000 | 132 fewer per 1000<br>(from 86 fewer to 165 fewer) |
| PE | 985<br>(1 study)<br>8 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 0 fewer to 0 more)[c] |
| Major bleeding | 985<br>(1 study)<br>8 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 1.97<br>(1.2 to 3.24) | 45 per 1000 | 44 more per 1000<br>(from 9 more to 101 more) |
| Wound haematoma | 985<br>(1 study) | VERY LOW[a,b]<br>due to risk of bias, | Peto OR 1.92 | 2 per 1000 | 2 more per 1000<br>(from 2 fewer to 35 more) |

| 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 (low dose; pre-op) (95% CI) |
| | 8 days | imprecision | (0.2 to 18.53) | | |

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 Zero events in both arms. Risk difference calculated in Review Manager.

**Table 52: Clinical evidence summary: LMWH (low dose; post-operation) 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 (low dose; post-op) (95% CI) |
| All-cause mortality | 976 (1 study) 8 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.14 (0.01 to 2.17) | 4 per 1000 | 4 fewer per 1000 (from 4 fewer to 5 more) |
| DVT (symptomatic and asymptomatic) | 674 (1 study) 8 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.55 (0.39 to 0.76) | 240 per 1000 | 108 fewer per 1000 (from 58 fewer to 146 fewer) |
| PE | 976 (1 study) 8 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 0 fewer to 0 more)[c] |
| Major bleeding | 976 (1 study) 8 days | LOW[a,b] due to risk of bias, imprecision | RR 1.46 (0.86 to 2.48) | 45 per 1000 | 21 more per 1000 (from 6 fewer to 67 more) |
| Wound haematoma | 976 (1 study) 8 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.96 (0.2 to 18.87) | 2 per 1000 | 2 more per 1000 (from 2 fewer to 35 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

| 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 (low dose; post-op) (95% CI) |
| risk of bias<br>b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.<br>c Zero events in both arms. Risk difference calculated in Review Manager. | | | | | |

**Table 53: Clinical evidence summary: LMWH (low dose; pre-operation) versus LMWH (low dose; post-operation)**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH (low dose; post-op) | Risk difference with LMWH (low dose; pre-op) (95% CI) |
| All-cause mortality | 983<br>(1 study)<br>8 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | Peto OR 7.27<br>(0.45 to 116.42) | 0 per 1000 | -[a] |
| DVT (symptomatic and asymptomatic) | 673<br>(1 study)<br>8 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | RR 0.82<br>(0.54 to 1.23) | 131 per 1000 | 24 fewer per 1000<br>(from 60 fewer to 30 more) |
| PE | 983<br>(1 study)<br>8 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 0 fewer to 0 more)[d] |
| Major bleeding | 983<br>(1 study)<br>8 days | LOW[b,c]<br>due to risk of bias, imprecision | RR 1.35<br>(0.87 to 2.09) | 66 per 1000 | 23 more per 1000<br>(from 9 fewer to 72 more) |
| Wound haematomas | 983<br>(1 study)<br>8 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | Peto OR 0.98<br>(0.14 to 6.99) | 4 per 1000 | 0 fewer per 1000<br>(from 4 fewer to 24 more) |
| a Absolute effects could not be calculated due to zero events in the control arm<br>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 | | | | | |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH (low dose; post-op) | Risk difference with LMWH (low dose; pre-op) (95% CI) |
| c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.<br>d Zero events in both arms. Risk difference calculated in Review Manager. | | | | | |

**Table 54: 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) |
| Major bleeding | 201<br>(1 study)<br>15 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | Peto OR 7.46<br>(0.15 to 376.15) | Not estimable[a] | -[a] |
| a Absolute effects could not be calculated due to zero events in one of the arms<br>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<br>c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. | | | | | |

**Table 55: Clinical evidence summary: LMWH (low dose; standard duration) + AES versus AES (above-knee)**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with AES alone | Risk difference with LMWH (low dose) + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 190<br>(1 study)<br>8-10 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.69<br>(0.47 to 1.00) | 454 per 1000 | 141 fewer per 1000<br>(from 240 fewer to 0 more) |
| PE | 190<br>(1 study)<br>8-10 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 1.04<br>(0.06 to 16.81) | 5 per 1000 | 0 more per 1000<br>(from 5 fewer to 79 more) |
| Fatal PE | 190 | VERY LOW[a,b] | Peto OR | Not estimable[c] | -[c] |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with AES alone | Risk difference with LMWH (low dose) + AES (95% CI) |
| | (1 study)<br>8-10 days | due to risk of bias, imprecision | 7.71 (0.15 to 398.09) | | |

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 effects could not be calculated due to zero events in one of the arms

**Table 56: Clinical evidence summary: LMWH (low dose; standard duration) + AES 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 (length unspecified) | Risk difference with LMWH (low dose) + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 167<br>(1 study)<br>14 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.62 (0.40 to 0.97) | 419 per 1000 | 159 fewer per 1000<br>(from 13 fewer to 251 fewer) |
| PE | 167<br>(1 study)<br>90 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 20 fewer to 20 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 Zero events in both arms. Risk difference calculated in Review Manager.

**Table 57: Clinical evidence summary: LMWH (low dose; standard duration) versus LMWH (standard dose; standard duration)**

| Outcomes | No of Participants | Quality of the evidence | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | (studies) Follow up | (GRADE) | effect (95% CI) | Risk with LMWH (standard dose) | Risk difference with LMWH (low dose) (95% CI) |
|---|---|---|---|---|---|
| Major bleeding | 202<br>(1 study)<br>15 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.52<br>(0.05 to 5.06) | 20 per 1000 | 9 fewer per 1000<br>(from 19 fewer to 72 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 58: Clinical evidence summary: LMWH (low dose; standard duration) + AES versus LMWH (standard dose; standard duration) + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH (standard dose) + AES | Risk difference with LMWH (low dose) + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 161<br>(1 study)<br>90 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.77<br>(0.48 to 1.24) | 338 per 1000 | 78 fewer per 1000<br>(from 176 fewer to 81 more) |
| PE | 161<br>(1 study)<br>90 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.13<br>(0 to 6.74) | 12 per 1000 | 11 fewer per 1000<br>(from 13 fewer to 66 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 59: Clinical evidence summary: LMWH (variable 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 Control | Risk difference with *LMWH (variable dose) versus no prophylaxis (95% CI) |
| Major bleeding | 200<br>(1 study)<br>45 days | VERY LOW[c,d,e]<br>due to risk of bias, indirectness, | Not estimable[b] | Not estimable[b] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[a] |

| 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 (variable dose) versus no prophylaxis (95% CI) |
| | | imprecision | | | |

a Risk difference calculated in Review Manager
b Zero events in both arms
c 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
d The majority of the evidence was based on indirect comparisons
e Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

**Table 60: Clinical evidence summary: LMWH (variable dose; standard duration) + AES versus foot pump + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Foot pump + AES | Risk difference with LMWH (variable dose) + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 191 (1 study) 45 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 2.06 (0.53 to 8.01) | 31 per 1000 | 33 more per 1000 (from 15 fewer to 217 more) |
| PE | 200 (1 study) 45 days | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | Not estimable[3] | Not estimable[c] | 0 fewer per 1000 (from 20 fewer to 20 more)[c] |
| Fatal PE | 200 (1 study) 45 days | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 20 fewer to 20 more)[c] |
| Heparin-induced thrombocytopaenia (45 days) | 200 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.39 (0.15 to 372.38) | 0 per 1000 | -[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

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Foot pump + AES | Risk difference with LMWH (variable dose) + AES (95% CI) |

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.
d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
e Absolute effects could not be calculated due to zero events in control arm

**Table 61: 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) |
| DVT (symptomatic and asymptomatic) | 243 (2 studies) not reported | VERY LOW[a,b,c,d] due to risk of bias, inconsistency, indirectness, imprecision | RR 0.62 (0.31 to 1.23) | 504 per 1000 | 191 fewer per 1000 (from 348 fewer to 116 more) |
| Major bleeding | 167 (2 studies) not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Peto OR 7.20 (0.72 to 71.86) | 0 per 1000 | -[e] |
| Wound haematomas | 143 (1 study) not reported | LOW[a] due to risk of bias, indirectness | Peto OR 7.10 (2.28 to 22.15) | 13 per 1000 | 74 more per 1000 (from 17 more to 217 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.
d Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.
e Absolute effects could not be calculated due to zero events in control arm

**Table 62: Clinical evidence summary: UFH (extended duration) versus UFH (standard duration)**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with UFH (standard duration) | Risk difference with UFH (extended duration) (95% CI) |
| DVT (symptomatic and asymptomatic) | 61 (1 study) 45 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.57 (0.18 to 1.81) | 214 per 1000 | 92 fewer per 1000 (from 176 fewer to 174 more) |
| Major bleeding | 66 (1 study) 45 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 60 fewer to 60 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 Zero events in both arms. Risk difference calculated in Review Manager.

**Table 63: Clinical evidence summary: UFH 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 UFH (95% CI) |
| DVT (symptomatic and asymptomatic) | 37 (1 study) 7 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.24 (0.05 to 1.13) | 333 per 1000 | 253 fewer per 1000 (from 317 fewer to 43 more) |
| PE | 37 (1 study) 7 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Peto OR 0.10 (0 to 5.16) | 83 per 1000 | 74 fewer per 1000 (from 83 fewer to 236 more) |
| Fatal PE | 37 (1 study) 7 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 0.76 (0.05 to 11.39) | 83 per 1000 | 20 fewer per 1000 (from 79 fewer to 866 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 Aspirin | Risk difference with UFH (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 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 64: Clinical evidence summary: UFH + AES (length unspecified) 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 + AES (95% CI) |
| All-cause mortality | 67 (1 study) time-point not reported | VERY LOW[b,c] due to indirectness, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000 (from 60 fewer to 60 more)[a] |
| DVT (symptomatic and asymptomatic) | 60 (1 study) 10 days | HIGH | RR 0.37 (0.19 to 0.71) | 679 per 1000 | 427 fewer per 1000 (from 197 fewer to 550 fewer) |
| PE | 67 (1 study) time-point not reported | VERY LOW[b,c] due to indirectness, imprecision | RR 2.74 (0.3 to 25.05) | 31 per 1000 | 54 more per 1000 (from 22 fewer to 752 more) |
| Major bleeding | 67 (1 study) time-point not reported | VERY LOW[b,c,e] due to risk of bias, indirectness, imprecision | OR 7.20 (0.72 to 71.86) | 0 per 1000 | -[d] |

a Zero events in both arms. Risk difference calculated in Review Manager.
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
e 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 65: 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) |
| Major bleeding | 330 (2 studies) 11-17 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.57 (0.47 to 122.16) | 0 per 1000 | - |
| Wound haematoma | 167 (1 study) 11 days | LOW[b] due to imprecision | RR 2.96 (0.31 to 27.92) | 12 per 1000 | 24 more per 1000 (from 8 fewer to 324 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 66: Clinical evidence summary: Fondaparinux + 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 alone | Risk difference with Fondaparinux + AES (95% CI) |
| All-cause mortality | 163 (1 study) 17 days | VERY LOW[b,d] due to risk of bias, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000 (from 20 fewer to 20 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 Absolute effects could not be calculated due to zero events in the control arm
d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 67: Clinical evidence summary: Fondaparinux + IPCD + AES versus IPCD + AES**

| Outcomes | No of | Quality of the evidence | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | effect (95% CI) | Risk with IPCD + AES | Risk difference with Fondaparinux + IPCD + AES (95% CI) |
|---|---|---|---|---|---|
| DVT (symptomatic and asymptomatic) | 167 (1 study) 11 days | LOW[a] due to imprecision | RR 0.99 (0.33 to 2.94) | 72 per 1000 | 1 fewer per 1000 (from 48 fewer to 140 more) |
| PE | 167 (1 study) 11 days | LOW[a] due to imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000 (from 20 fewer to 20 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 68: Clinical evidence summary: Fondaparinux + AES versus fondaparinux**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux | Risk difference with Fondaparinux + AES (95% CI) |
| All-cause mortality | 795 (1 study) 35-49 days | VERY LOW[a,b] due to risk of bias, imprecision | OR 0.38 (0.05 to 2.7) | 7 per 1000 | 5 fewer per 1000 (from 7 fewer to 12 more) |
| Major bleeding | 795 (1 study) 35-49 days | VERY LOW[a,b] due to risk of bias, imprecision | OR 0.14 (0 to 7.05) | 2 per 1000 | 2 fewer per 1000 (from 2 fewer to 15 more) |
| Fatal PE | 795 (1 study) 35-49 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | -[c] |
| Clinically relevant non-major bleeding | 795 (1 study) 35-49 days | VERY LOW[a,b] due to risk of bias, imprecision | OR 0.14 (0 to 7.05) | 50 per 1000 | 42 fewer per 1000 (from 50 fewer to 219 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.

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux | Risk difference with Fondaparinux + AES (95% CI) |
| c Zero events in both arms. Risk difference calculated in Review Manager. | | | | | |

**Table 69: Clinical evidence summary: Fondaparinux + IPCD + AES versus VKA + IPCD + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with VKA + IPCD + AES | Risk difference with Fondaparinux + IPCD + AES (95% CI) |
| All-cause mortality | 118 (1 study) 30 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] |
| DVT (symptomatic and asymptomatic) | 118 (1 study) 30 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] |
| PE | 118 (1 study) 30 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.<br>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<br>c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. | | | | | |

**Table 70: Clinical evidence summary: IPCD 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 IPCD (95% CI) |
| DVT (symptomatic and asymptomatic) | 400 (2 studies) 7-14 days | MODERATE[a] due to risk of bias | RR 0.53 (0.4 to 0.69) | 498 per 1000 | 234 fewer per 1000 (from 154 fewer to 299 fewer) |

| 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 IPCD (95% CI) |
| PE | 310<br>(1 study)<br>14 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 1.04<br>(0.06 to 16.7) | 6 per 1000 | 0 more per 1000<br>(from 6 fewer to 90 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 71: Clinical evidence summary: VKA versus no 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) |
| Major bleeding | 138<br>(1 study)<br>10 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000<br>(from 30 fewer to 30 more)[a] |
| Clinically relevant non-major bleeding | 95<br>(1 study)<br>7 days | VERY LOW[b,c]<br>due to risk of bias, indirectness, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000<br>(from 40 fewer to 40 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
d The majority of the evidence was based on indirect comparisons

**Table 72: Clinical evidence summary: VKA (extended duration) versus VKA (standard duration)**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with VKA (standard duration) | Risk difference with VKA (extended duration) (95% CI) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with VKA (standard duration) | Risk difference with VKA (extended duration) (95% CI) |
| All-cause mortality | 360 (1 study) 28 days | VERY LOW[b,c] due to risk of bias, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000 (from 10 fewer to 10 more)[a] |
| DVT (symptomatic and asymptomatic) | 360 (1 study) 28 days | VERY LOW[b,c] due to risk of bias, imprecision | RR 0.36 (0.1 to 1.33) | 45 per 1000 | 29 fewer per 1000 (from 41 fewer to 15 more) |
| PE | 360 (1 study) 28 days | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 0.13 (0 to 6.52) | 6 per 1000 | 5 fewer per 1000 (from 6 fewer to 30 more) |
| Major bleeding | 360 (1 study) 28 days | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 7.07 (0.14 to 356.89) | 0 per 1000 | -[d] |

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.
d Absolute effects could not be calculated due to zero events in the control arm.

**Table 73: Clinical evidence summary: IPCD 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 IPCD (95% CI) |
| DVT (symptomatic and asymptomatic) | 138 (1 study) 10 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1 (0.47 to 2.11) | 167 per 1000 | 0 fewer per 1000 (from 88 fewer to 185 more) |
| PE | 138 (1 study) | VERY LOW[a,b] due to risk of bias, | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 30 fewer to 30 more)[c] |

| 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 IPCD (95% CI) |
| | 10 days | imprecision | | | |

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 Zero events in both arms. Risk difference calculated in Review Manager.

**Table 74: Clinical evidence summary: IPCD + AES versus VKA + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with VKA + AES | Risk difference with IPCD + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 296<br>(2 studies)<br>8 days | VERY LOW[a,b,c]<br>due to risk of bias, inconsistency, imprecision | RR 0.49<br>(0.13 to 1.83) | 297 per 1000 | 152 fewer per 1000<br>(from 259 fewer to 247 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 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 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 75: Clinical evidence summary: Foot pump + 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 alone | Risk difference with Foot pump + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 79<br>(1 study)<br>6-9 days | MODERATE[a]<br>due to risk of bias | RR 0.26<br>(0.09 to 0.7) | 400 per 1000 | 296 fewer per 1000<br>(from 120 fewer to 364 fewer) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with AES alone | Risk difference with Foot pump + AES (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 | | | | | |

**Table 76: Clinical evidence summary: Foot pump + 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 Foot pump + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 132 (1 study) 42 days | LOW[a] due to risk of bias, imprecision | RR 0.38 (0.19 to 0.76) | 354 per 1000 | 219 fewer per 1000 (from 85 fewer to 287 fewer) |
| a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. | | | | | |

**Table 77: Additional data that could not be meta-analysed: Fondaparinux + AES versus fondaparinux for people undergoing elective hip replacement**

| Study | Outcome | Time-point | Fondaparinux + AES | Fondaparinux | Risk of bias |
|---|---|---|---|---|---|
| Cohen 2007[59] | Quality of life; EQ-5D; Health state score | Screening (before surgery) | 0.21 (-0.59-1.00) | 0.16 (-0.59-1.00) | Very low risk of bias* |
| | | Last day of treatment (5-9 days/35-49 days) | 0.59 (-0.59-1.00) | 0.59 (-0.43-1.00) | Very low risk of bias* |
| | | Follow-up (35-49 days) | 0.76 (-0.17-1.00) | 0.71 (-0.09-1.00) | Very low risk of bias* |
| | Quality of life; EQ-5D; Overall health status | Screening (before surgery) | 65 (0-100) | 60 (0-100) | Very low risk of bias* |
| | | Last day of treatment (5-9 days/35-49 days) | 70 (20-100) | 70 (6-100) | Very low risk of bias* |
| | | Follow-up (35-49 days) | 80 (0-100) | 80 (3-100) | Very low risk of bias* |

**This is not a formal GRADE assessment as results were not reported in a manner amenable to analysis.*

## 26.4 Economic evidence

**Published literature**

Thirty-two economic studies, in 35 publications, relating to this review question were identified but were excluded due limited applicability, methodological limitations, a combination of limited applicability and methodological limitations or the availability of the newly developed economic model for this update which was considered to be more applicable evidence.[10 ,32 ,33 ,39 ,47 ,68 ,70 ,75 ,79 ,80 ,117 ,119 ,126 ,128 ,197 ,206-208 ,214 ,224 ,226 ,228-230 ,246 ,253-255 ,259 ,281 ,282 ,305 ,320 ,321 ,329] These included 3 NICE TAs, 2 evidence review group [ERG] reports and the CG92 model for standard duration and post discharge prophylaxis. Also, 10 of these publications were previously included in CG46.[10 ,32 ,33 ,68 ,70 ,79 ,119 ,126 ,197 ,253] All excluded studies are listed in appendix O, with reasons for exclusion given.

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

**New cost-effectiveness analysis**

The committee considered the available evidence of cost effectiveness of prophylaxis strategies for people admitted for elective hip replacement (eTHR). The original guideline (CG92) model was considered but it was considered that it required updating given the availability of more recent trial data and the exclusion of the some of the older studies that were included in the CG92 NMAs from the current updated NMAs. The original model also included some interventions that are not routinely used in current practice including high doses of aspirin, VKA and UFH. The committee also discussed that since the publication of CG92, three TAs covering the use of DOACs in this population have also been published; the latest in 2012.[228-230] It was agreed that it would be more convenient for clinicians to be able to consult a single source for recommendation regarding the most cost-effective prophylaxis strategy for this population. Moreover, as the size of the population covered by this review question is very large; which means that changes to more costly prophylaxis options would lead to substantial resource implications, the committee agreed that this question should be prioritised for economic modelling. This was also considered to be necessary given the current variation in clinical practice across the NHS in England. Hence, de-novo economic model was developed to address the question about the cost-effectiveness of different VTE prophylaxis strategies (alone or in combination) in people admitted for eTHR. A summary of the model is presented below and a detailed description can be found in appendix P in the full guideline.

**Model overview**

A cost-utility analysis was undertaken in Microsoft Excel® where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services (PSS) perspective. A Markov model was constructed in order to estimate the costs and QALYs associated with different VTE prophylaxis strategies. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance[231] Uncertainty was explored through probabilistic and deterministic sensitivity analyses. The time horizon used was lifetime.

**Population**

The population entering the model are adults who are admitted to hospital for an eTHR. The cohort characteristics were based on the data reported in the National Joint Registry 13th annual report;[36] which represented data collected up to December 2015 in England, Wales, Northern Ireland and the Isle of Man. The mean age of this population was 68.7 years and 40% were male.

**Comparators**

Sixteen prophylaxis strategies were selected for inclusion based on the availability of evidence from the clinical review, direct and network meta-analyses (N)MAs and discussion with the committee around which regimens are considered to be relevant to current clinical practice in the UK. These were:

1. LMWH (std,std) + AEs
2. LMWH (std,extd)+ AEs
3. Fondaparinux+ AES
4. Foot pump + AES
5. IPCD
6. AES (above knee)
7. Foot pump
8. AES
9. LMWH (std,std)
10. LMWH (std,extd)
11. Aspirin (std duration)
12. LMWH (std, std) + Aspirin (extd duration)
13. Dabigatran
14. Apixaban
15. Rivaroxaban
16. No prophylaxis

**Model structure**

The model consists of a simple decision tree covering the acute phase from admission up to 90 days post-operatively, to cover the period included in the definition of hospital-acquired VTE, followed by a Markov chain for the remaining model time horizon. The structure is repeated for each prophylaxis strategy.

The acute phase of the model is represented by a decision tree consisting of the primary clinical events: DVT (symptomatic proximal, symptomatic distal, asymptomatic proximal and asymptomatic distal), non-fata PE, fatal PE, Surgical site bleeding, non-surgical site bleeding (gastrointestinal (GI) bleeding, intracranial haemorrhage (ICH)/haemorrhagic stroke, other major bleeding), fatal major bleeding (MB), clinically-relevant non-major bleeding (CRNMB) and heparin-induced thrombocytopaenia (HIT).The structure of the decision tree is presented in **Figure 1.**

The long-term part is represented by a Markov cohort model. Individuals enter the model in one of the following states; based on where they end up at the end of the 90 days post-operatively: Well, post-symptomatic proximal DVT, post-symptomatic distal DVT, post-asymptomatic proximal DVT, post-asymptomatic distal DVT, post-PE, amputated post-HIT, disabled post-stroke, post-revision for infection. In the first two years, individuals in a post-VTE state can develop post-thrombotic syndrome (PTS). Those in the post-PE state can also develop chronic thromboembolic pulmonary hypertension (CTEPH). Transitioning to death is allowed from any state in the model. The structure of the Markov cohort model is illustrated in **Figure 2.**

**Model inputs**

The relative effects of treatments on the baseline transition probabilities were derived from clinical evidence identified in the systematic review undertaken for the guideline, the results of the NMA and supplemented by additional data sources as required. Health utility data were obtained from the literature. Cost inputs were obtained from recognized national sources such as the drug tariff, NHS reference costs and Personal Social Services Research Unit (PSSRU) publications. All inputs and assumptions made were validated by the committee.

**Sensitivity analysis**

A probabilistic analysis was carried out whereby distributions were assigned to model inputs in order to account for the uncertainty and capture its effect on model outputs. Additionally, a number of one-way sensitivity analyses were conducted whereby for each analysis one key model input was changed in order to explore the sensitivity of model results to changes in that parameter (Table 78).

**Table 78: One-way sensitivity analyses**

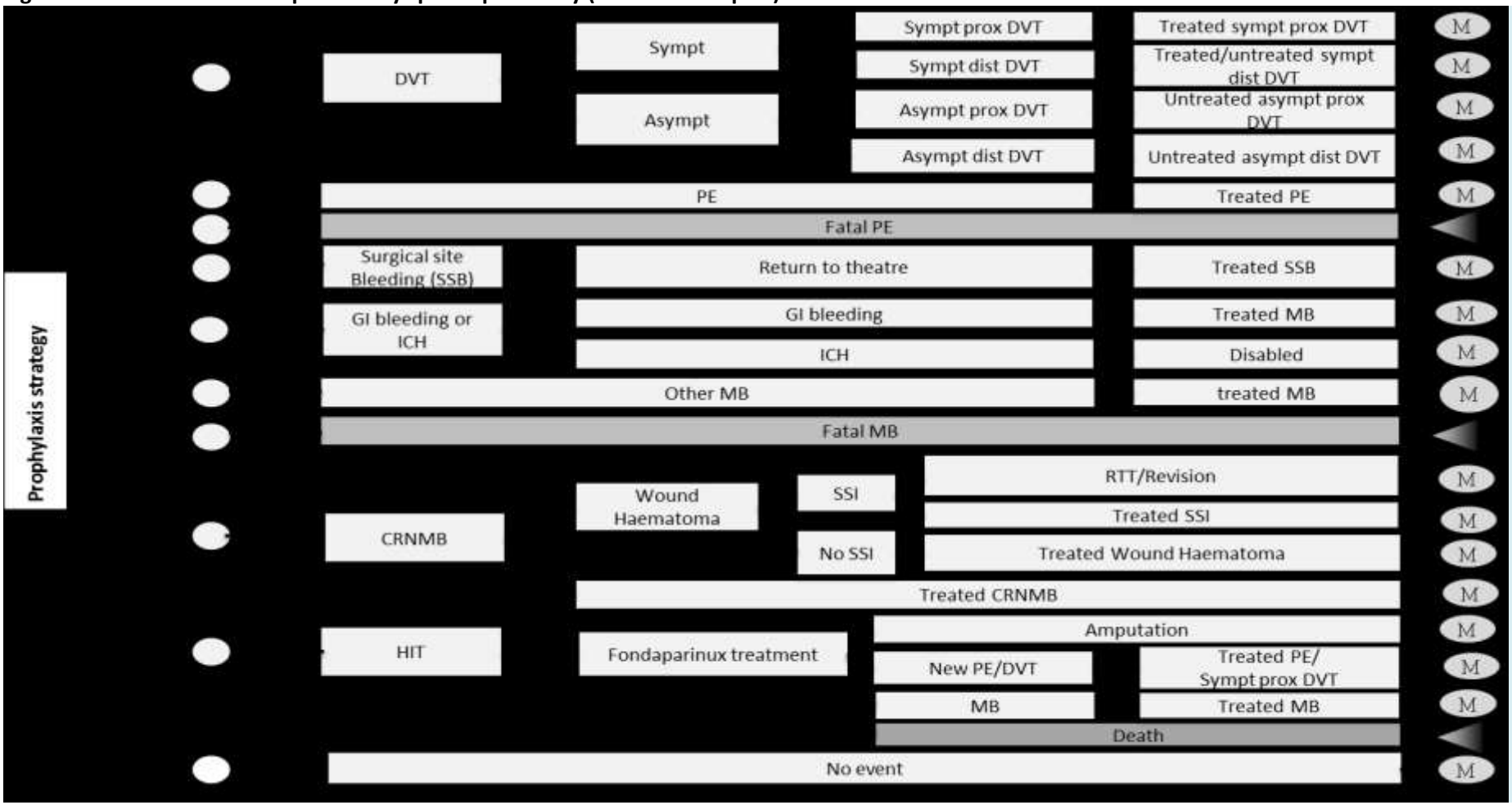
| | description | Base case input value | Alternative value for sensitivity analysis |
|---|---|---|---|
| SA1 | Cost-effectiveness threshold | £20,000 | £30,000 |
| SA2 | Discount rate for costs and QALYs | 3.5% | 1.5% |
| SA3 | Prophylaxis duration | Based on the RCTs included in the DVT NMA | based on summary of product characteristics (SmPC) |
| SA4 | Cohort starting age | eTHR: 68.7 years (a) | 40 years |
| SA5 | Cohort body weight | NJR cohort mean body weight(a) | Cohort body weight distribution calculated based on the NJR cohort BMI distribution (a) and average height for a UK male (1.75m) and female (1.62 m) (b) |
| SA6 | All costs +10% | See appendix P | Costs increased by 10% |
| SA7 | All costs -10% | See appendix P | Costs decreased by 10% |
| SA8 | Timing of VTE and MB events | Based on committee expert opinion | Based on data from Warwick 2007[308] |
| SA9 | Risk of VTE recurrence after :<br><br>Treated DVT<br>PE | Assumption based on committee opinion<br><br>0%<br>0% | Calculated based on data from TA245 manufacturer submissions<br><br>2.74%<br>0.26% |
| SA10 | Costs of pharmacological prophylaxis | Calculated assuming no wastage | Calculated taking possible wastage into account |
| SA11 | Risk of DVT when using LMWH (std/std) followed by aspirin | Calculated using the odds ratio from the PE network<br><br>0.05% | Calculated using the odds ratio from Anderson 2013 for the outcome Proximal DVT<br><br>3.68% |

*Abbreviations: eTHR: elective total hip replacement; NMA: network meta-analysis; SA: sensitivity analysis*

*(a) Source: national Joint Registry[36]*

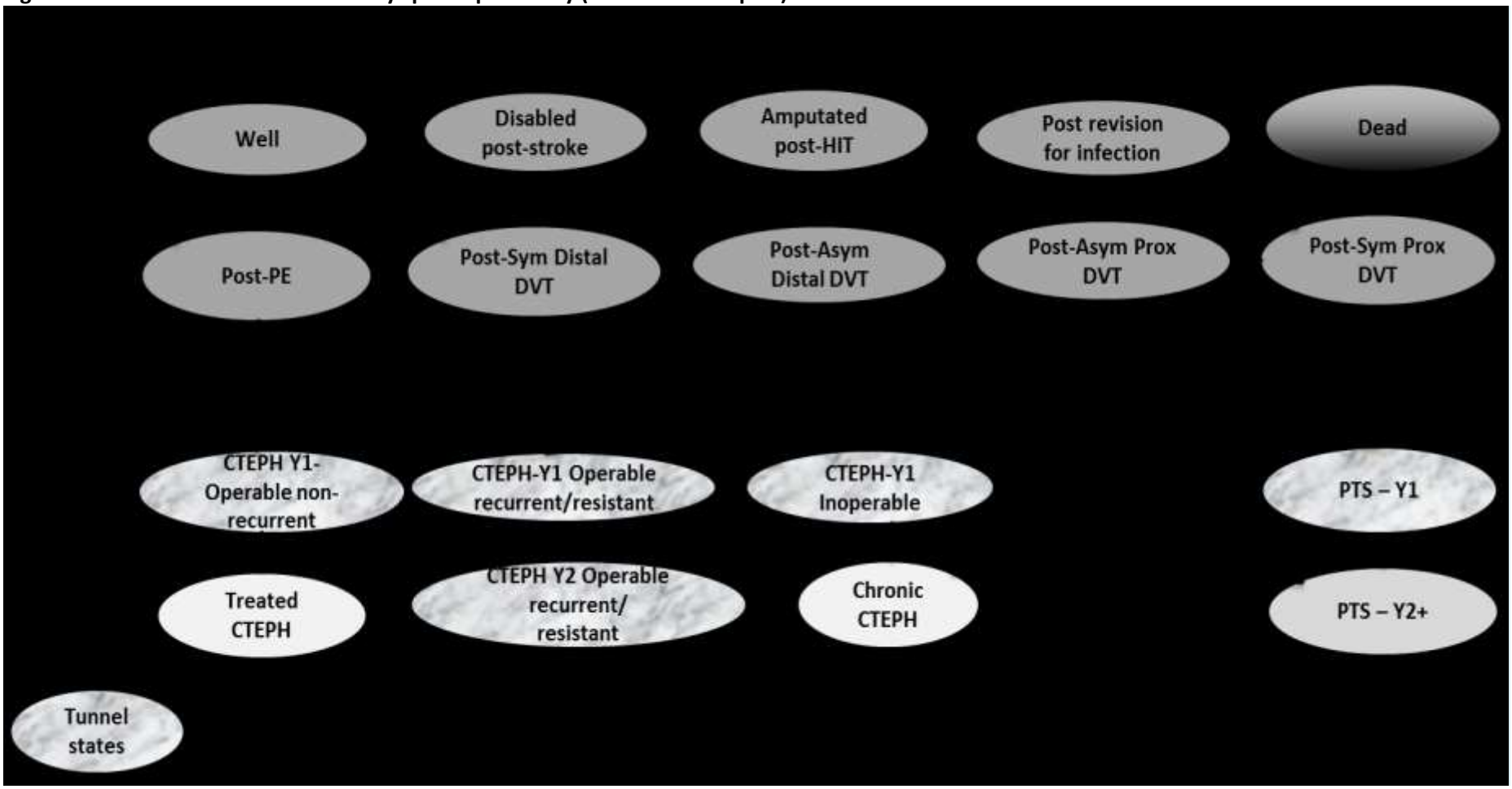
*(b) Source: ONS [237]*

**Figure 1: Model structure up to 90 days post-operatively (Decision tree part)**




*Abbreviations: Asympt: asymptomatic; Dist: distal; DVT: Deep vein thrombosis; GI: gastrointestinal; HIT: heparin-induced thrombocytopaenia; ICH: intracranial haemorrhage; MB: major bleeding; PE: pulmonary embolism; Prox: proximal; RTT: return to theatre; SSB: surgical site bleeding, SSI: surgical site infection; Sympt: symptomatic*

**Figure 2: Model structure after 90 days post-operatively (Markov model part)**




*Abbreviations: Asympt: asymptomatic; CTEPH: chronic thrombo-embolic pulmonary hypertension; DVT: Deep vein thrombosis; HIT: heparin-induced thrombocytopaenia; PE: pulmonary embolism; Prox: proximal; PTS: post-thrombotic syndrome; Sympt: symptomatic*

**Results**

***Base case***

The results of the base case analysis are presented in Table 79 and Figure 3. These show that the most effective strategy in terms of QALYs-gained is LMWH (standard dose, standard duration) for 10 days followed by aspirin for 28 days (extended duration), with mean discounted QALYs per patient of 10.293 (95% CI: 8.02 to 12.00) over life-time time horizon. The least effective strategy was aspirin (standard duration); with 9.42 QALYs (95% CI: 6.50 to 11.59); which also had the highest mean discounted total cost £1,687 (95% CI: £157 to £4,039) per person over life-time time horizon. The least costly prophylaxis strategy was AES with mean discounted cost per person of £299 (95% CI: £102 to £793) followed by LMWH (standard dose, standard duration) +aspirin (extended duration) strategy with mean discounted cost of £311 (95% CI: £148 to £1437).

The incremental net monetary benefit (INMB) vs the comparator (LMWH [standard, dose, standard duration]+ AES) was calculated for all strategies at a cost-effectiveness threshold of £20,000 per QALY-gained. Based on the INMB, the most cost-effective strategy (the one with the highest INMB) was found to be LMWH (standard dose, standard duration) for 10 days followed by aspirin for 28 days; with mean INMB of £530 (95% CI: -£784 to £1,103). This was followed by LMWH (standard dose, extended duration) +AES (unspecified length) with mean INMB of £42.

The full ranking based on the mean INMB of each strategy; together with the 95% confidence intervals that were calculated probabilistically, are presented in Table 79. Based on the rank of the mean INMB; all strategies except AES (above knee), foot pump and aspirin (standard duration) were more cost effective than no prophylaxis.

Extended duration LMWH, solely or in combination with AES, ranked higher compared to standard duration. AES (unspecified length) were on average the most cost-effective mechanical intervention in this population. The DOACs (rivaroxaban, apixaban and dabigatran) were dominant compared to no prophylaxis but were dominated by the model comparator (LMWH [standard dose, standard duration]+AES). Of the three DOACs, rivaroxaban was cost-effective compared to apixaban with an ICER of £12,242 per QALY-gained and both rivaroxaban and apixaban were dominant (more effective and less costly) compared to dabigatran.

***Sensitivity analysis***

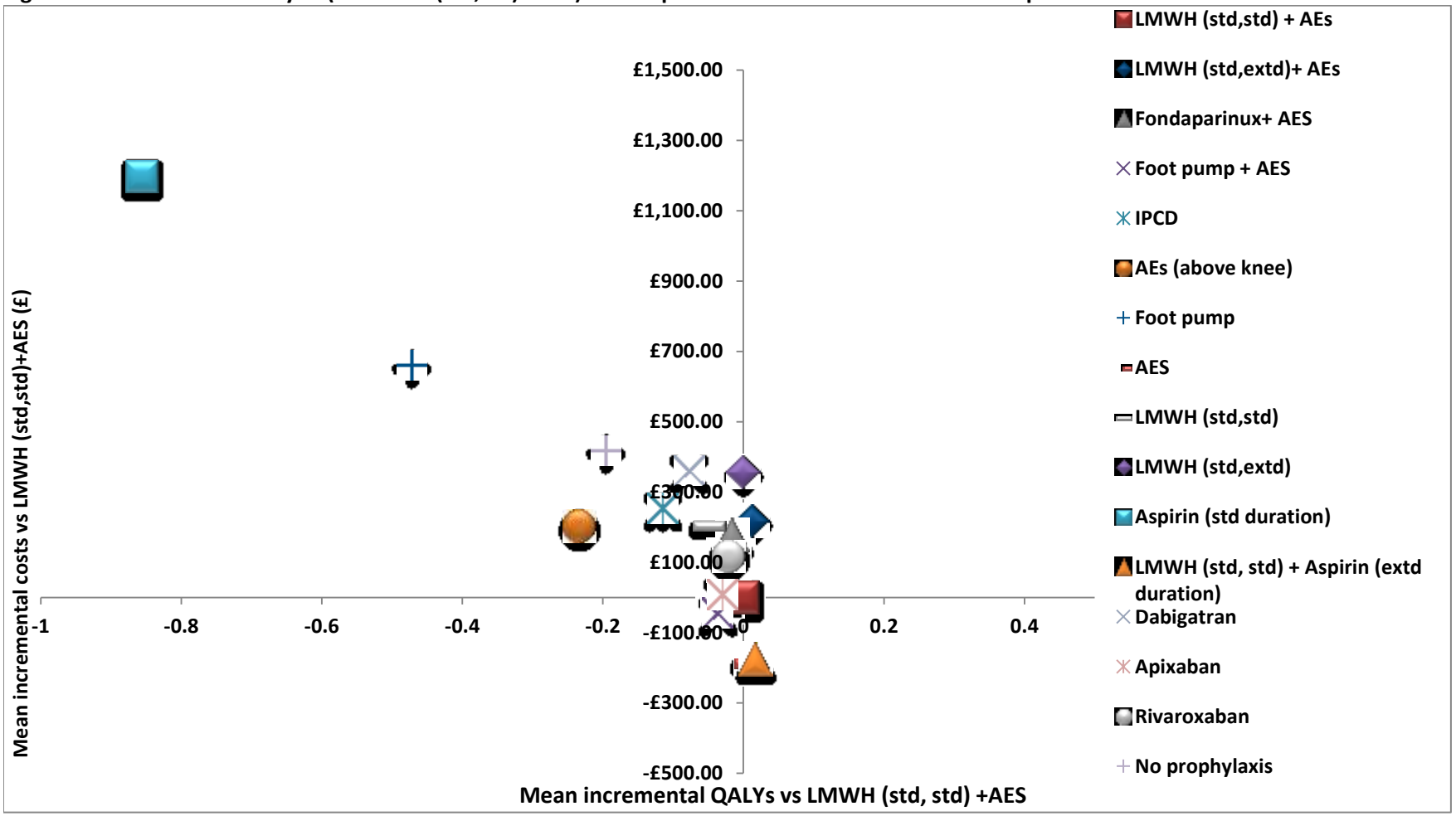
In all the SAs undertaken, the most cost-effective option (LMWH [standard dose, standard duration) followed by aspirin (extended duration) did not change.

**Table 79: Probabilistic base case analysis results for elective total hip replacement (eTHR) population**

| Intervention | Mean discounted QALYs (95% CI) | Mean Discounted Costs (95% CI) | Incremental QALYs vs LMWH+ AEs (95% CI) | Incremental costs vs LMWH+ AEs (95% CI) | Mean INMB at £20K (95% CI) | Probability most CE option | Rank (95% CI) |
|---|---|---|---|---|---|---|---|
| **LMWH (std,std) + AEs** | **10.28** (8.01 to 11.98) | **£489** (£350 to £832) | **0.000** (0.000 to 0.000) | **£0** (£0 to £0) | **£0** (£0 to £0) | 0.1% | **4** (3, 11) |
| **LMWH (std,extd)+ AEs** | **10.29** (8.02 to 12.00) | **£706** (£509 to £1,376) | **0.013** (-0.004 to 0.030) | **£217** (-£42 to £694) | **£36** (-£745 to £484) | 0.6% | **2** (2, 12) |
| **Fondaparinux+ AES** | **10.26** (7.98 to 11.96) | **£665** (£336 to £1,563) | **-0.015** (-0.112 to 0.013) | **£176** (-£92 to £800) | **-£478** (-£2,618 to £278) | 0.2% | **6** (3, 15) |
| **Foot pump + AES** | **10.24** (7.99 to 11.94) | **£445** (£209 to £926) | **-0.036** (-0.182 to 0.012) | **-£44** (-£329 to £398) | **-£684** (-£3,930 to £478) | 0.6% | **9** (2, 15) |
| **IPCD** | **10.16** (7.86 to 11.91) | **£742** (£255 to £1,968) | **-0.115** (-0.681 to 0.011) | **£253** (-£246 to £1,455) | **-£2,550** (-£14,733 to £396) | 0.1% | **12** (4, 15) |
| **AEs (above knee)** | **10.04** (7.35 to 11.93) | **£691** (£119 to £3,765) | **-0.234** (-2.197 to 0.027) | **£202** (-£424 to £3,310) | **-£4,873** (-£46,725 to £861) | 13.2% | **14** (1, 16) |
| **Foot pump** | **9.80** (6.96 to 11.77) | **£1,150** (£161 to £4,054) | **-0.472** (-2.681 to 0.015) | **£661** (-£344 to £3,578) | **-£10,104** (-£57,043 to £590) | 1.4% | **15** (2, 16) |
| **AES** | **10.27** (8.01 to 11.97) | **£299** (£102 to £793) | **-0.009** (-0.103 to 0.022) | **-£189** (-£460 to £261) | **£5** (-£2,106 to £781) | 8.4% | **3** (1, 14) |
| **LMWH (std,std)** | **10.23** (7.95 to 11.94) | **£691** (£375 to £1,413) | **-0.048** (-0.283 to 0.009) | **£202** (-£44 to £767) | **-£1,162** (-£6,266 to £197) | 0.0% | **10** (6, 13) |
| **LMWH (std,extd)** | **10.27** (7.98 to 11.98) | **£844** (£528 to £1,582) | **0.000** (-0.070 to 0.025) | **£356** (£24 to £954) | **-£361** (-£2,042 to £349) | 0.1% | **5** (4, 13) |
| **Aspirin (std duration)** | **9.42** (6.50 to 11.59) | **£1,687** (£157 to £4,039) | **-0.856** (-3.179 to 0.009) | **£1,198** (-£390 to £3,610) | **-£18,312** (-£66,988 to £479) | 0.7% | **16** (2, 16) |
| **LMWH (std, std) + Aspirin (extd duration)** | **10.29** (8.02 to 12.00) | **£311** (£148 to £1437) | **0.018** (0.003 to 0.036) | **-£178** (-£548 to £781) | **£530** (-£784 to £1,103) | 72.0% | **1** (1, 11) |
| **Dabigatran** | **10.20** (7.93 to 11.94) | **£849** (£319 to £1,957) | **-0.077** (-0.465 to 0.010) | **£360** (-£122 to £1,331) | **-£1,903** (-£10,144 to £254) | 0.0% | **11** (5, 15) |
| **Apixaban** | **10.25** (7.96 to 11.97) | **£497** (£163 to £1,588) | **-0.030** (-0.270 to 0.022) | **£8** (-£302 to £895) | **-£598** (-£6,089 to £632) | 2.2% | **8** (2, 14) |
| **Rivaroxaban** | **10.25** (7.97 to 11.97) | **£606** (£227 to £1,452) | **-0.021** (-0.190 to 0.019) | **£117** (-£234 to £814) | **-£529** (-£4,385 to £514) | 0.4% | **7** (2, 13) |
| **No prophylaxis** | **10.08** (7.80 to 11.82) | **£908** (£297 to £2,185) | **-0.196** (-0.885 to -0.008) | **£419** (-£195 to £1,677) | **-£4,336** (-£19,297 to -£95) | 0.0% | **13** (10, 16) |

*Abbreviations: AEs: anti-embolism stockings; CE: cost effective; CI: confidence interval; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; INMB: incremental net monetary benefit; LMWH: low molecular weight heparin; QALYs: quality-adjusted life-years; std: standard*

**Figure 3: Incremental analysis (vs LMWH (std,std)+ AES) results presented on the cost effectiveness plane**



*Abbreviations: Abbreviations: AES: anti-embolism stockings; CE: cost-effective; CI: confidence interval; eTHR: elective total hip replacement; extd: extended; INMB: incremental net monetary benefit; IPCD: intermittent pneumatic compression device; LMWH: low molecular weight heparin; std: standard; QALYs: quality-adjusted life-years.*

**Discussion**

**Interpretation and limitations**

The results of this analysis support the conclusion of the clinical review, direct and network meta-analyses that VTE prophylaxis is effective compared to no prophylaxis. However, the choice of a prophylaxis strategy is not clear cut. This is likely to be the result of the uncertainty around the relative effectiveness estimates for the different interventions; which was clearly shown in the results of the NMAs that informed the economic model.

Nevertheless, based on the results of this economic model; combined prophylaxis, despite being more costly in terms of intervention costs, is likely to be the most cost-effective option for individuals undergoing eTHR with the two most cost-effective options representing a combination of either two pharmacological or one pharmacological and one mechanical option. Of the DOACs considered; rivaroxaban dominated dabigatran and was cost-effective compared to apixaban with an ICER of £12,242 per QALY-gained. This was in line with the results of TA170 where rivaroxaban was found to dominate dabigatran.[229] A recent analysis funded by the NIHR found that rivaroxaban dominated dabigatran and was cost-effective compared to apixaban with an ICER of £114 per QALY gained.[281] TA245 also found that dabigatran was dominated, apixaban was extendedly dominated and rivaroxaban had an ICER of £22,123 per QALY-gained compared to fondaparinux.[230]

Of the mechanical prophylaxis options considered in the analysis; AES-based strategies were more cost-effective compared to IPCD and foot pump. However, it was not possible to directly compare the length of AES (knee vs thigh length) in terms of cost effectiveness as there were no effectiveness data for the knee-length stockings to allow its inclusion in this analysis. Additionally, results were conflicting for AES in general; with those where length was unspecified ranking better than no prophylaxis while those with above-knee length being worse compared to no prophylaxis.

This model was an update of the CG92 model; so we attempted to address the limitations of that model which were highlighted by the orthopaedic surgeons' community in a number of publications. One limitation was the use of relative effectiveness from the DVT NMA for the PE outcomes. To address this, we used the PE NMA results for all strategies except where the strategy was not in the network (foot pump + AES). Nevertheless, we have verified the proportionality assumption with the committee and externally validated it using the published observational data analysis that used NJR data;[153] where the ratio of the relative effectiveness of LMWH vs aspirin for the DVT outcome was found to be the same as for the PE outcome.

Another issue was the lack of differentiation between proximal and distal DVT. We have addressed this issue by differentiating between the proximal and distal DVT for both symptomatic and asymptomatic events. We also allowed for different probabilities of progressing from each of these DVT outcomes to PTS; to acknowledge the fact that progression from treated and untreated DVT to PTS would occur with different probabilities. We emphasised the fact that asymptomatic DVT does not have an impact on costs and outcomes in the short term as it is not diagnosed in practice and its only consequence in the model is its future progression to PTS. There was also a concern regarding the baseline risk used in the model which was based on data from the no prophylaxis arm in the RCTs. This was criticised as it was not considered to be reflective of current incidence of VTE; with some trials dating back to the 70s, especially as practice has changed in terms of encouraging early mobilisation as well as the difference in surgical techniques. Based on this, we have used LMWH +AES as our model comparator and obtained its baseline risk data from observational cohort studies that used the UK NJR data.[153]

However; this updated analysis may have some limitations. Due to lack of data on either DVT or PE outcomes for some strategies, an assumption still had to be made about the equivalence of relative effectiveness on the DVT and PE outcomes for these strategies. However, we have limited this only

to instances where data was available for one of these outcomes but not for the other; as explained earlier. The relative effectiveness of the strategy LMWH (std, std)+ aspirin (extd duration) in relation to the DVT outcome was based on its relative effectiveness obtained from the PE NMA. This assumption could have affected the results but we have tested it in a sensitivity analysis which showed that the model results were robust to this change.

Additionally; in this analysis, aspirin (standard duration) came as the least favourable option and indeed, on average, worse than no prophylaxis. This is a highly uncertain conclusion as the relative effectiveness of aspirin in this population was based on a single small and outdated trial that the orthopaedic subgroup did not consider to be reflective of current clinical practice; nevertheless, this was the only trial for aspirin in this population. It was also noted that the findings of this trial are at odds with their clinical experience and the observational studies that used the NJR data in this population [153].

A limitation of this analysis is that the relative safety of aspirin compared to LMWH was based on an observational cohort analysis based on NJR data. [153] This was due to the lack of any randomised controlled trials that report major bleeding outcomes for aspirin in these populations. However, as the data for MB from trials are likely to be imprecisely estimated, due to the rarity of these events, it was considered that this would be an appropriate source of relative effectiveness for a safety outcome.

**Generalisability to other populations/settings**
This analysis has been undertaken from a UK NHS and PSS perspective; hence its results might not be generalisable beyond these settings. The population modelled also represents a cohort whose characteristics might be different from eTHR cohorts in other countries.

**Conclusions**
In people undergoing elective total hip replacement (e[THR]), VTE prophylaxis appears to be cost-effective compared to no prophylaxis. A strategy consisting of LMWH (standard dose) for 10 days followed by aspirin for 28 days was the most cost-effective. This result was robust to changes in the model input parameters. LMWH-based strategies that use extended duration LMWH or its combination with AES are more cost effective compared to LMWH standard duration alone or in combination with AES. Rivaroxaban was found to be the most cost-effective of the DOACs considered in this analysis.

## 26.5 Evidence statements

**Clinical**

**Pairwise meta-analysis statements**

**Pharmacological interventions versus pharmacological interventions**

*LMWH (standard dose; standard duration)*

LMWH at a standard dose for a standard duration was compared with unfractionated heparin, with the outcomes of all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and wound haematoma reported across four studies. There was a suggested possible clinical benefit of LMWH in terms of all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and haematoma. However there was inconsistency surrounding all results with each also possibly being consistent with no difference, and all-cause mortality, DVT and wound haematoma also being consistent with clinical harm. All of the evidence was graded very low due to risk of bias, inconsistency and indirectness.

LMWH at a standard dose for a standard duration was compared with VKA, with the outcomes of DVT (symptomatic and asymptomatic), major bleeding and wound haematoma reported in one study. There was a suggested possible clinical harm of LMWH for all these outcomes. However inconsistency around the results means the result could also be no difference or in the case of major bleeding, also clinical benefit. All of the evidence was graded very low due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration was compared with dabigatran, with the outcomes of all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and clinically relevant non-major bleeding reported across two studies. There was a suggested possible clinical benefit of LMWH in terms of major bleeding, however the imprecision around this estimate was also consistent with no difference. There was a suggested possible clinical harm of LMWH in terms of all-cause mortality and no clinical difference in terms of DVT (symptomatic and asymptomatic), PE and clinically relevant non-major bleeding; however there was considerable uncertainty around these results. The quality of the evidence ranged from very low to moderate due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration was compared with apixaban, with the outcomes of all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE, clinically relevant non-major bleeding and heparin-induced thrombocytopaenia reported in one study. There was suggested possible clinical benefit of LMWH in terms of all-cause mortality and fatal PE, although these findings were very imprecise and therefore could also be consistent with no difference or clinical harm. High quality evidence demonstrated clinical harm of LMWH in terms of DVT (symptomatic and asymptomatic). Low quality evidence suggested possible clinical harm of LMWH in terms of PE and heparin-induced thrombocytopaenia, although these findings were very imprecise and therefore could also be consistent with no difference or clinical benefit. There was no clinical difference in terms of major bleeding and clinically relevant non-major bleeding. The quality of the evidence ranged from low to high due to imprecision. The outcome with high-quality evidence was DVT (symptomatic and asymptomatic).

LMWH at a standard dose for a standard duration was compared with rivaroxaban, with the outcomes of all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, clinically relevant non-major bleeding and wound infection reported in one study. Moderate quality, precise evidence demonstrated clinical harm of LMWH in terms of all-cause mortality and DVT (symptomatic and asymptomatic). Very low quality evidence suggested possible clinical harm in terms of PE;

however this result was very imprecise. There was no clinical difference in terms of major bleeding, clinically relevant non-major bleeding and wound infection, although the imprecision around these results was also consistent with both benefit and harm. The quality of evidence ranged from very low to moderate due to risk of bias, imprecision and indirectness.

LMWH at a standard dose for a standard duration was compared with fondaparinux, with the outcomes of major bleeding and wound haematoma was reported in two studies. There was suggested possible clinical benefit of LMWH in terms of major bleeding, although this finding was also consistent with no difference. There was suggested no clinical difference in terms of wound haematoma, however imprecision around this estimate was also consistent with both benefit and harm. The quality of evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

LMWH at a standard dose for a standard duration was compared with no prophylaxis in four studies; the outcomes DVT (symptomatic and asymptomatic), PE, major bleeding, wound haematoma and wound infection were reported. Precise evidence showed clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic) and PE; and clinical harm of LMWH in terms of major bleeding. Possible clinical harm was suggested for LMWH in terms of wound haematoma and wound infection, however these results were imprecise. The quality of evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

*LMWH (standard dose; extended duration)*

LMWH at a standard dose for an extended duration was compared with rivaroxaban, with the outcomes of all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, clinically relevant non-major bleeding and wound infection reported in one study. There was suggested possible clinical benefit of LMWH in terms of all-cause mortality and PE, however these results were seriously imprecise meaning they could also be consistent with no difference or harm. Moderate quality evidence showed clinical harm of LMWH in terms of DVT (symptomatic and asymptomatic). No clinical difference was seen in terms of major bleeding, clinically relevant non-major bleeding and wound infection, however there was uncertainty around these results. The quality of the evidence ranged from very low to moderate due to risk of bias and imprecision.

LMWH at a standard dose for an extended duration was compared with LMWH at a standard dose followed by aspirin for an extended duration, with the outcomes of all-cause mortality, PE, major bleeding, fatal PE, clinically relevant non-major bleeding and wound infection reported in one study. There was possible clinical harm of LMWH in terms of all-cause mortality, PE, major bleeding and clinically relevant non-major bleeding, however these results were associated with very serious imprecision and therefore could also be consistent with no difference or clinical benefit. No clinical difference was noted for fatal PE and wound infection, although again these results were very imprecise. The quality of the evidence ranged from very low to low due to risk of bias 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, DVT (symptomatic and asymptomatic), PE, major bleeding, heparin-induced thrombocytopaenia and wound haematoma were reported across three studies. Moderate quality evidence showed clinical benefit of LMWH at an extended duration in terms of DVT (symptomatic and asymptomatic). Very low quality evidence suggested a possible clinical benefit of this same intervention in terms of PE and major bleeding, although these findings were very imprecise and could also be associated with no difference and clinical harm. There suggested possible clinical harm of LMWH at an extended duration in terms of heparin-induced thrombocytopaenia. Again these last three outcomes were imprecise. There was no clinical difference in terms of all-cause mortality and wound haematoma. The quality of the evidence ranged from very low to moderate due to risk of bias and imprecision.

*LMWH (high dose; standard duration)*

LMWH at a high dose for a standard duration was compared with unfractionated heparin, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE and wound haematoma, reported in one study. There was a suggested possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic), PE, major bleeding. However the imprecision around these results suggested they could also be associated with no difference. There was suggested possible clinical harm of LMWH in terms of all-cause mortality, wound haematoma and no clinical difference in terms of fatal PE. Again there was imprecision associated with these results. The quality of the evidence ranged from very low to low due to risk of bias, inconsistency, indirectness and imprecision.

LMWH at a high dose for a standard duration was compared with fondaparinux the outcome of major bleeding was reported in one study. There was a reported possible clinical benefit of LMWH for this outcome, but the imprecision around the result was also associated with no difference. Quality of the evidence was low due risk of bias and imprecision.

LMWH at a high dose for a standard duration was compared with VKA, the outcomes of all-cause mortality, PE and major bleeding reported in one study. There was a possible clinical benefit of LMWH in regards to all-cause mortality and PE; and possible clinical harm of LMWH in terms of major bleeding. However the evidence for all three outcomes was very uncertain and findings could have been associated with no difference, benefit or harm. The quality of evidence was very low due to risk of bias and imprecision.

LMWH at a high dose for a standard duration was compared with LMWH at a standard dose for a standard duration, the outcomes reported were all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and wound haematoma reported in one study. There was a suggested clinical benefit of LMWH at a high dose in terms of DVT (symptomatic and asymptomatic) and PE and possible clinical harm in terms of all-cause mortality, major bleeding and wound haematoma. However there was uncertainty surrounding the results for all five outcomes. The quality of the evidence ranged from very low to low due to risk of bias, imprecision and inconsistency.

LMWH at a high dose for a standard duration was compared to no prophylaxis, the outcomes DVT (symptomatic and asymptomatic), PE and major bleeding were reported in one study. moderate quality evidence showed clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic). Very low quality evidence suggested possible clinical benefit of LMWH in terms of major bleeding and no clinical difference for PE. However there was uncertainty associated with the PE and major bleeding results. Quality of evidence ranged from very low to moderate due to risk of bias, indirectness and imprecision.

*LMWH (high dose; extended duration)*

LMWH at a high dose for an extended duration was compared with VKA, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and major bleeding reported in one study. Low quality evidence showed clinical benefit of LMWH in terms of major bleeding. Low to very low quality evidence suggested possible clinical benefit in terms of all-cause mortality, DVT (symptomatic and asymptomatic) and PE. There was considerable uncertainty around the morality and VTE results. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

*LMWH (low dose; standard duration; pre-operation)*

LMWH at a low dose for a standard duration from pre-operation was compared with VKA, all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and wound haematoma reported in one study. Low quality evidence showed clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic). There was possible clinical harm of LMWH in terms of major

bleeding and wound haematoma, however there was uncertainty around these results. There was no clinical difference for all-cause mortality, although this finding was also consistent with both clinical benefit and harm. 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 from pre-operation was compared with LMWH at a low dose at a standard duration from post-operation, all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and wound haematoma reported in one study. There was reported possible clinical harm of LMWH at a low dose from pre-operation in terms of all-cause mortality and major bleeding, although there was uncertainty around these results. There was no clinical difference in terms of DVT (symptomatic and asymptomatic) and PE and wound haematoma, although there was uncertainty around these results. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

*LMWH (low dose; standard duration; post-operation)*

LMWH at a low dose for a standard duration from pre-operation was compared with VKA, all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and wound haematoma reported in one study. There was reported possible clinical benefit LMWH in terms of all-cause mortality and DVT (symptomatic and asymptomatic), possible clinical harm of LMWH in terms of major bleeding and wound haematoma and no clinical difference in terms of PE. However all five outcomes were imprecise and therefore there is uncertainty around these results. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

*LMWH (low dose; standard duration)*

LMWH at a low dose for a standard duration was compared with LMWH at a standard dose for a standard duration, major bleeding was reported in one study. There was reported possible clinical benefit of LMWH, but the uncertainty around this result was also associated with no difference or clinical harm. The quality of the evidence was very low due to risk of bias and imprecision.

LMWH at low dose for a standard duration was compared with no prophylaxis, major bleeding was reported in one study. There was reported possible clinical harm of LMWH, but the uncertainty around this result was also associated with no difference or clinical benefit. The quality of the evidence was very low due to risk of bias and imprecision.

*LMWH (variable dose; standard duration)*

LMWH at a variable dose for a standard duration was compared with no prophylaxis, major bleeding was reported in one study. There was reported no clinical difference, but there was imprecision around this result. Quality of the evidence was very low due to risk of bias, indirectness and imprecision.

*UFH (standard duration and extended duration)*

UFH was compared with no prophylaxis, the outcomes DVT (symptomatic and asymptomatic), major bleeding and wound haematomas were reported across two studies. There was possible clinical benefit of UFH in terms of DVT (symptomatic and asymptomatic), however the imprecision around this result was also consistent with no difference. There was clinical harm of UFH in terms of wound haematomas and possible clinical harm of UFH in terms of major bleeding, however the bleeding result was associated with very serious imprecision. The quality of the evidence was very low to low due to risk of bias, indirectness, inconsistency and imprecision.

UFH was compared with aspirin, outcomes DVT (symptomatic and asymptomatic), PE and fatal PE were reported in one study. There was possible clinical benefit of UFH for all of the outcomes reported. However the DVT outcome was also consistent with no difference, and the PE outcomes

were so uncertain that they were consistent with both no difference and clinical harm. The quality of the evidence was very low due to risk of bias, imprecision and indirectness.

UFH for an extended duration was compared with standard duration course of UFH, outcomes DVT (symptomatic and asymptomatic) and major bleeding were reported in one study. There was possible clinical benefit of UFH for an extended duration in terms of DVT (symptomatic and asymptomatic) and no clinical difference in terms of major bleeding, however both of these results had serious uncertainty. The quality of the evidence was very low due to risk of bias and imprecision.

*VKA (standard duration and extended duration)*

VKA (standard duration) was compared with no prophylaxis, outcomes major bleeding and clinically relevant non-major bleeding was reported in one study. There no clinical difference for these outcomes, although the quality of the evidence was very low due to risk of bias, imprecision and indirectness.

VKA at an extended duration was compared with VKA at a standard duration, outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and major bleeding were reported in one study. There was possible clinical benefit of VKA at an extended duration in terms of DVT (symptomatic and asymptomatic) and PE, possible clinical harm of VKA at an extended duration in terms of major bleeding and no clinical difference in terms of all-cause mortality. However all four of these outcomes had high uncertainty around the results. The quality of the evidence was all very low due to risk of bias and imprecision.

*Fondaparinux*

Fondaparinux was compared to no prophylaxis; the outcomes major bleeding and wound haematoma were reported across two studies. There was possible clinical harm of fondaparinux in terms of major bleeding and wound haematoma. However both of these results had such high uncertainty that they may have been consistent with no difference and clinical benefit. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

**Pharmacological interventions versus mechanical interventions**

*LMWH (standard dose)*

LMWH at a standard dose for a standard duration was compared with IPCD, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was suggested no clinical difference between the two interventions for the reported outcomes. However imprecision was so serious as to be consistent with both clinical benefit or clinical harm. The quality of the evidence was low due to imprecision.

LMWH at a standard dose for a standard duration was compared with foot pump, the outcomes DVT (symptomatic and asymptomatic), PE and fatal PE were reported in one study. There was suggested possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic) and PE, however there was uncertainty around these results. There was no clinical difference for the outcome of fatal PE, although this outcome was also uncertain. The quality of the evidence was all graded very low due to risk of bias and imprecision.

**Mechanical interventions versus mechanical interventions**

IPCD was compared with no prophylaxis, outcomes DVT (symptomatic and asymptomatic) and PE were reported across two studies. There was suggested clinical benefit of IPCD in terms of DVT (symptomatic and asymptomatic) and no clinical difference for PE, although there was uncertainty around these results. The quality of the evidence ranged from very low to moderate due to risk of bias and imprecision.

**Mechanical interventions versus pharmacological interventions**

IPCD was compared with VKA, outcomes DVT (symptomatic and asymptomatic) and PE. There no clinical difference for these outcomes, although the quality of the evidence was very low due to risk of bias and imprecision.

**Combination interventions versus combination interventions or single-prophylaxis agents**

*LMWH (standard dose)*

LMWH at a standard dose for a standard duration in combination with AES was compared with no prophylaxis, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. High quality evidence showed clinical benefit of LMWH in combination with AES in terms of DVT (symptomatic and asymptomatic), and low quality evidence suggested possible clinical benefit of LMWH in combination with AES in terms of PE, although this finding was very uncertain.

LMWH at a standard dose for a standard duration in combination with AES was compared with LMWH at a standard dose for a standard duration, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was suggested possible clinical benefit of LMWH in combination with AES for both outcomes, although the very serious imprecision reflected that the result could also be consistent with both no difference or clinical harm. The quality of the evidence was low due to imprecision.

LMWH at a standard dose for a standard duration in combination with AES was compared with AES alone, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic) and PE were reported across three studies. There was suggested possible clinical benefit of LMWH in combination AES in terms of DVT (symptomatic and asymptomatic), although this finding could also be consistent with no difference. No clinical difference was suggested in terms of all-cause mortality and PE, but these results had considerable uncertainty. The quality of the evidence ranged from very low to low due to risk of bias, inconsistency and imprecision.

LMWH at a standard dose for a standard duration in combination with IPCD and AES was compared with IPCD and AES, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was no clinical difference between the two interventions for both of the outcomes, however there was uncertainty around these results. The quality of the evidence was low due to imprecision.

LMWH at a standard dose for a standard duration in combination with AES was compared with fondaparinux in combination with AES, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, fatal PE and major bleeding were reported in one study. There was clinical harm of LMWH in combination with AES in terms of DVT (symptomatic and asymptomatic). Possible clinical harm of LMWH in combination with AES was suggested in terms of all-cause mortality, however this result was very uncertain. There was possible clinical benefit of LMWH in combination with AES in terms of major bleeding and no clinical difference in terms of PE and fatal PE, however all three of these outcomes were associated with harm, no difference and benefit due to uncertainty. The quality of the evidence was very low due to risk of bias, imprecision and indirectness.

LMWH at a standard dose for a standard duration in combination with IPCD and AES was compared with fondaparinux in combination with IPCD and AES, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was reported no clinical difference between the two interventions, however there was uncertainty around these results. The quality of the evidence was low due to imprecision.

LMWH at a standard dose for an extended duration in combination with AES was compared with LMWH at a standard dose for a standard duration in combination with AES, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was reported possible

clinical benefit of LMWH for an extended duration in combination with AES for both of the outcomes, however the uncertainty around these results was also consistent with no difference. The quality of the evidence was low due to risk of bias and imprecision.

*LMWH (high dose)*

LMWH at a high dose for a standard duration in combination with AES was compared with fondaparinux in combination with AES, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and fatal PE were reported in one study. There was reported possible clinical benefit of LMWH at a high dose in combination with AES in terms of all-cause mortality and PE, but possible clinical harm in terms of DVT (symptomatic and asymptomatic) and fatal PE. However all four of these results were associated with considerable uncertainty. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

*LMWH (low dose)*

LMWH at a low dose for a standard duration in combination with AES was compared with AES (above-knee), the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was possible clinical benefit of LMWH at a low dose in combination with AES in terms of DVT (symptomatic and asymptomatic) and no clinical difference for PE, however there was uncertainty around these results. LMWH at a low dose for a standard duration in combination with AES was also compared with AES (length unspecified) in one study, reporting the same outcomes of DVT (symptomatic and asymptomatic). The clinical effects were the same for this comparison for the outcomes reported for the comparison with AES (above-knee). 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 in combination with AES was compared with LMWH at a standard dose for a standard duration in combination with AES, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was possible clinical benefit of LMWH at a low dose in combination with AES in terms of PE and no clinical difference for DVT (symptomatic and asymptomatic), however the uncertainty associated with both these results was large enough to be consistent with benefit and harm. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

*LMWH (variable dose)*

LMWH at a variable dose for a standard duration in combination with AES was compared with foot pump in combination AES, the outcomes DVT (symptomatic and asymptomatic), PE, fatal PE and heparin-induced thrombocytopaenia were reported in one study. There was possible clinical harm of a LMWH at a variable dose with AES in terms of DVT (symptomatic and asymptomatic) and heparin-induced thrombocytopaenia. There was no clinical difference in terms of PE and fatal PE. However the variance associated with all of these results was very wide and could be consistent with either benefit or harm. All the evidence was graded very low due to risk of bias, imprecision and indirectness.

*UFH*

UFH in combination with AES was compared with AES (length unspecified), outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and major bleeding were reported in one study. High quality evidence showed clinical benefit of UFH in combination with AES in terms of DVT (symptomatic and asymptomatic). Very low quality evidence suggested possible clinical harm of UFH in combination with AES in terms of PE and major bleeding. There was no clinical difference for all-cause mortality. There was considerable uncertainty around all the non-DVT results. The quality of the evidence ranged from very low to high due to risk of bias, indirectness and imprecision. The outcome with evidence of high quality was DVT (symptomatic and asymptomatic).

*Fondaparinux*

Fondaparinux in combination with AES was compared with AES, outcome of all-cause mortality was reported in one study. There was no clinical difference; however this result had considerable uncertainty associated with it. One study evaluated the addition of IPCD to both interventions, the outcomes were DVT (symptomatic and asymptomatic) and PE were reported. There was no clinical difference for these two outcomes, although again these findings were considerably uncertain. One study evaluated the use of fondaparinux in the comparator arm reporting the outcomes all-cause mortality, major bleeding, fatal PE and clinically relevant non-major bleeding. There was possible clinical benefit of fondaparinux in combination with AES in terms of all-cause mortality, major bleeding and clinically relevant non-major bleeding, however the results were so uncertain as to also consistent with no difference or clinical harm. There was no clinical difference for fatal PE. The quality of the evidence across these three comparisons ranged from very low to low due to risk of bias and imprecision.

Fondaparinux in combination with IPCD was compared with VKA in combination with IPCD, outcomes all-cause mortality, DVT (symptomatic and asymptomatic) and PE were reported in one study. There was no clinical difference for all of the outcomes, however there was uncertainty around these results. The quality of the evidence was very low due to risk of bias and imprecision.

*Combination mechanical interventions*

IPCD in combination with AES was compared with VKA in combination with AES, the outcome DVT (symptomatic and asymptomatic) was reported in two studies. There was possible clinical benefit of IPCD in combination with AES for this outcome, however this was so uncertain that the result could also be consistent with no difference or clinical harm. The quality of the evidence was very low due to risk of bias, inconsistency and imprecision.

Foot pump in combination with AES was compared with AES (length unspecified), DVT (symptomatic and asymptomatic was reported in one study. Moderate quality, precise evidence showed clinical benefit of foot pump with AES. One study evaluated similar interventions with UFH in combination with AES in the comparator arm. The same outcome of DVT (symptomatic and asymptomatic) was reported, with possible clinical benefit of foot pump in combination with AES in terms of this outcome. However this finding was also consistent with no difference due to uncertainty. The quality of evidence ranged from low to moderate due to risk of bias and imprecision.

**Additional study data**

One study that evaluated fondaparinux in combination with AES was compared with fondaparinux and reported a quality of life measure (EQ-5D) outcome measuring from screening (before surgery) to follow-up at 35-49 days. This data could not be meta-analysed but the outcome data reported suggests a similar increase in quality of life between the various time-points in both intervention groups.

**Network meta-analysis statements**

*DVT (symptomatic and asymptomatic)*

42 studies were included in the network meta-analysis (NMA) for the outcome of DVT (symptomatic and asymptomatic), involving 26 treatments. Treatments included no VTE prophylaxis, pharmacological and mechanical interventions as single agents as well as combination interventions of both pharmacological and mechanical interventions. Results from the network meta-analysis presented rivaroxaban, fondaparinux in combination with AES and LMWH at standard dose and high dose for varying durations (standard duration and extended duration) in combination with AES as the most clinically effective interventions in terms of the outcome of DVT (symptomatic and

asymptomatic). The least clinically effective interventions were no prophylaxis, UFH for an extended duration, IPCD and foot pump. Eight inconsistencies were identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a considerable amount of uncertainty around the rank-point estimates with very wide credible intervals.

PE

30 studies were included in the NMA for the outcome of PE, involving 23 treatments. Treatments included no VTE prophylaxis, pharmacological and mechanical interventions as single agents as well as combination interventions of both pharmacological and mechanical interventions. Results from the network meta-analysis presented LMWH at a standard dose for a standard duration followed by a course of aspirin for an extended duration, LMWH at a high dose for an extended duration and LMWH at standard dose and high dose for varying durations (standard duration and extended duration) in combination with AES as the most clinically effective interventions in terms of the outcome of PE. The least clinically effective interventions were aspirin for a standard duration, foot pump and no prophylaxis. One inconsistency was identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a considerable amount of uncertainty around the rank-point estimates with very wide credible intervals.

*Major bleeding*

24 studies were included in the NMA for the outcome of major bleeding, involving 15 treatments. Treatments included no VTE prophylaxis and pharmacological interventions (mechanical interventions were combined with no prophylaxis as the assumption was made that these interventions do not contribute to bleeding risk). Results from the network meta-analysis presented LMWH at a standard dose for a standard duration followed by a course of aspirin for an extended duration, no prophylaxis, VKA at a standard duration as the most clinically effective interventions in terms of major bleeding. The least clinically effective interventions were VKA at an extended duration, fondaparinux and dabigatran. One inconsistency was identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a high amount of uncertainty around the rank-point estimates with very wide credible intervals across a majority of the interventions.

***Economic***

- One original cost-utility analysis found that, in people admitted for elective total hip replacement surgery, the following interventions were cost-effective (having positive incremental net monetary benefit [INMB]) compared to LMWH (standard dose, standard duration) +AEs: LMWH (standard dose, standard duration) + aspirin (extended duration) (INMB £530); LMWH (standard dose, extended duration)+ AEs (INMB £36) and AES (INMB: £5). This analysis was assessed as directly applicable with minor limitations.

## 26.6 Recommendations and link to evidence

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| **Recommendations** | **1.5.8 Offer VTE prophylaxis to people undergoing elective hip replacement surgery whose risk of VTE outweighs their risk of bleeding.** |

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| | **Choose any one of:**<br>• **LMWH[h] for 10 days followed by aspirin[i] (75 or 150 mg) for a further 28 days**<br>• **LMWH[j] for 28 days combined with anti-embolism stockings (until discharge)**<br>• **Rivaroxaban[k]. 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]**<br><br>**1.5.9 Consider one of the following if none of the options in recommendation 1.5.8 can be used:**<br>• **Apixaban[l] 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).]**<br>• **Dabigatran etexilate[m], 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).]**<br><br>**1.5.10 Consider anti-embolism stockings until discharge from hospital if pharmacological interventions are contraindicated in people** |

[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), 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.

[j] 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.

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

| | undergoing elective hip replacement surgery. [2018] |
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| **Research recommendation** | **9. 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?**<br><br>**10. What is the clinical and cost effectiveness of aspirin alone for VTE prophylaxis in people undergoing elective total hip replacement surgery?** |
| 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), fatal PE (7–90 days from hospital discharge), major bleeding (up to 45 days from hospital discharge) and surgical site haematoma (up to 45 days from hospital discharge) as critical outcomes.<br><br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) and infection (duration of study) as important outcomes.<br><br>Three network meta-analyses were conducted for this population, evaluating the outcomes DVT (symptomatic and asymptomatic), PE and major bleeding across numerous interventions.<br><br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Evidence from direct pairwise comparisons was included in the network meta-analyses for the elective hip replacement population. The quality of the pairwise comparisons ranged from very low to high due to risk of bias, imprecision, indirectness and inconsistency.<br><br>The DVT (symptomatic and asymptomatic) network evaluated 26 interventions, the PE network evaluated 23 interventions and the major bleeding network evaluated 14 interventions. Inconsistencies were identified in the DVT (symptomatic and asymptomatic), PE and major bleeding networks between the direct pairwise evidence and the NMA evidence, but there was good calibration for all the outcomes with small differences between the residual deviance and DIC values for the network meta-analysis models that were run. Wide credible intervals around the median network meta-analyses values present some uncertainty around the NMA results for all of the NMA outcomes. |
| Trade-off between clinical benefits and harms | The clinical evidence presented to the committee and orthopaedic subgroup informed the economic model that was developed. The committee's discussions on the clinical evidence guided the recommendations alongside discussions on the results of the economic model. The model evaluated cost effectiveness using clinical data from the network-meta analyses undertaken on the committee-specified critical outcomes of DVT (symptomatic and asymptomatic), PE, and major bleeding. The model also captured data from the included trials on additional outcomes such as symptomatic DVT and asymptomatic DVT, and more detailed bleeding outcomes such as surgical site bleeding, gastrointestinal bleeding, and wound haematoma.<br><br>When assessing the results of the analysis of the clinical data, the committee noted that the credible intervals for the NMA rankings were considerably wide, representing large uncertainty around the effects. For the DVT network credible intervals for the top ranked interventions ranged from 1–13 for the tightest CI and 1–25 for the widest. Similarly for the PE network the highest ranked interventions ranged from 1–13 and 1–20. The uncertainty around the results was even more |

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| | pronounced in the major bleeding network where the top ranked intervention had a CI spanning the entire range (1–15).<br><br>The committee noted that LMWH was often amongst the top ranked interventions when assessing only the clinical data for all three critical outcomes, particularly when used for an extended duration (28 days) and often when combined with anti-embolism stockings, as presented in the relevant trials identified. Rivaroxaban (duration specified from the British National Formulary) performed well when assessing DVT although less so for PE and major bleeding. Whilst discussing the data for rivaroxaban, the committee and orthopaedic subgroup also evaluated the evidence for the other DOACs (apixaban and dabigatran). They showed potential value when considered for DVT and PE, but performed less well when assessed for major bleeding. This is in line with widespread clinical concern about the bleeding risk associated with DOACs in orthopaedic populations. While fondaparinux ranked highly in the DVT network, it was not amongst the top ranked interventions for the PE and major bleeding outcomes and the committee noted that it is not widely used in clinical practice. The top ranked intervention for the clinical outcomes of PE and major bleeding was a combined pharmacological option of LMWH initially, followed by aspirin. The committee and orthopaedic subgroup discussed the current concerns in regards to the bleeding risk associated with aspirin, especially when used soon after surgery (when bleeding risk is highest). However they agreed that the use of aspirin after a 10-day course of LMWH would take into account the high early bleeding risk whilst providing clinical benefit in terms of the evaluated outcomes of PE and major bleeding. The durations for LMWH (10 days) and aspirin (28 days) are based on the evidence evaluated in the clinical trials.<br><br>The orthopaedic subgroup noted that current clinical practice by some orthopaedic surgeons includes the use of intermittent pneumatic compression devices post-operatively followed by the use of AES. The NMA results did not present any clear clinical benefit for using IPCDs. Modern developments in clinical practice include the encouragement of early mobilisation post-operation, and the use of IPCDs can potentially restrict mobility of patients who have undergone elective hip replacement surgery. |
| Trade-off between net clinical effects and costs | An original economic model was developed to assess the cost effectiveness of the prophylaxis options included in the clinical review NMAs. It models the outcomes from the NMAs and also differentiates between asymptomatic and symptomatic DVT. This takes into account that asymptomatic DVT does not have an impact on costs and outcomes in the short term as it is not diagnosed in practice and its only consequence in the model is its future progression to PTS.<br><br>Sixteen options were included in this model:<br>• Anti-embolism stockings (AES) (above knee)<br>• AES (length unspecified<br>• Apixaban<br>• Aspirin (standard duration)<br>• Dabigatran<br>• Fondaparinux+ AES<br>• Foot pump + AES<br>• Foot pump<br>• IPCD (sleeve length unspecified)<br>• LMWH (standard dose, standard duration)<br>• LMWH (standard dose, extended duration)<br>• LMWH (standard dose, standard duration) followed by Aspirin (extended duration)<br>• LMWH (standard dose, standard duration) + AES<br>• LMWH (standard dose, extended duration)+ AES<br>• No prophylaxis |

- Rivaroxaban

The model results showed that the most cost-effective option for this population is combined prophylaxis using LMWH (standard dose) for 10 days followed by aspirin for 28 days. This intervention had the highest mean incremental net monetary benefit (INMB) per patient compared to LMWH (standard dose, standard duration) + anti-embolism stockings (£530) at a cost-effectiveness threshold of £20,000 per QALY-gained. Compared to no prophylaxis, all prophylaxis options ranked higher except foot pump, anti-embolism stocking (above-knee) and aspirin (standard duration). A number of sensitivity analyses were presented to the committee including changing the cost effectiveness threshold to £30,000 per QALY gained; changing the discount rate for costs and QALYs to 1.5% and using the licensed duration where applicable rather than the average RCT duration.

The committee and the orthopaedic subgroup considered the results of the model and noted that the most cost-effective intervention, LMWH for 10 days followed by Aspirin for 28 days, had a high probability of being the most cost-effective option (72%). It was also the most cost-effective option in all sensitivity analyses. This result was in line with the findings from the MB and PE NMAs, where this intervention was ranked at the top. However, this intervention was not included in the DVT NMA as the only trial that included this regimen did not report DVT (symptomatic and asymptomatic) as an outcome but reported data for proximal DVT. Hence, in the economic model an assumption had to be made that the odds ratio from the PE NMA would be the same for the DVT outcome, which may have influenced the results. This assumption has been tested in a sensitivity analysis where the relative effectiveness of LMWH followed by aspirin on the DVT (symptomatic and asymptomatic) outcome was assumed to be the same as that for the outcome "proximal DVT" which was reported in the included trial. In this analysis, LMWH followed by aspirin retained its first rank. However, the committee noted that the evidence of efficacy for this intervention is based on a single trial, there is high uncertainty around the ranking of the interventions considered in the model with large and overlapping 95% confidence intervals around these ranks, and there are small differences in costs and QALYs among the included interventions. Hence, the committee opted to give a choice of prophylaxis options rather than only recommending this intervention as the most cost-effective intervention.

Of the LMWH-based strategies in the model, those with extended duration and in combination with AES appeared to be more cost-effective compared to the LMWH alone used for standard duration in this population, despite their higher cost compared to the other strategies in the model. This appeared to be driven by the higher incidence of symptomatic DVT and PE in this population.

The committee discussed that for patients who are unable to self-administer parenteral prophylaxis or may be needle-phobic, oral anticoagulants were considered to be the appropriate prophylaxis option. The committee and the orthopaedic subgroup noted that out of the three DOACs included in the model (rivaroxaban, apixaban and dabigatran), rivaroxaban dominated dabigatran and was cost-effective compared to apixaban (ICER: £12,242 per QALY-gained). Apixaban had higher probability of being the most cost-effective compared to rivaroxaban (2.2% versus 0.2%%; respectively); however there was more uncertainty around the rank of apixaban compared to that of rivaroxaban (95% CI around the mean rank 2 to 14 for apixaban and 2 to 13 for rivaroxaban). Additionally, apixaban had double the probability of being the least cost-effective option compared to rivaroxaban (0.16% vs 0.08%, respectively). The committee took this decision uncertainty into account and noted that the conclusion that rivaroxaban is on average more cost-effective than apixaban for people undergoing total hip replacement largely agreed with the findings of most of the previously published economic evaluations which have been selectively excluded from this review. It was in line with the results of TA170 where rivaroxaban was found to dominate dabigatran.[229] A recent analysis funded by the

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| | NIHR found that rivaroxaban dominated dabigatran and was cost-effective compared to apixaban with an ICER of £114 per QALY gained.[281] TA245 also found that dabigatran was dominated, apixaban was extendedly dominated and rivaroxaban had an ICER of £22,123 per QALY gained compared to fondaparinux.[230] Hence, the committee determined that it would be beneficial to standardise practice in order to minimise costs and reduce errors and, hence, recommend the most cost-effective DOAC, rivaroxaban. This would also minimise costs and reduce e. Apixaban and dabigatran already have current technology appraisal guidance associated with them and are, therefore, also recommended. However, as both were not cost effective compared to rivaroxaban, the committee decided that these options could only be considered if all the three recommended options are not suitable for the person (for example due to contraindications or issues related to patient preference).<br><br>For those with contraindications for pharmacological prophylaxis, the committee and the orthopaedic subgroup considered that AES appeared to be the more cost-effective option in this population compared to IPCDs or foot pumps alone. The committee however determined that this was contrary to the evidence from other populations (for example people with stroke and those undergoing elective knee replacements). The committee also noted the difficulty in using AES for the durations reported in the trials as this would not be practical in real-world situations. Hence, there is considerable uncertainty about whether the effects observed in the trials can be replicated in real world settings. It was not possible to specify the length of the AES to recommend as the included trials in the NMAs did not have knee-length AES to allow its inclusion in the model. The committee acknowledged that thigh-length AES are more costly and more difficult to fit which would require close monitoring by the nurses to ensure adherence, which again calls into question the possibility of replicating their effect in real-world settings. However, the committee and orthopaedic subgroup decided that where pharmacological options are contraindicated, AES is an acceptable prophylaxis strategy. |
| Other considerations | The committee noted that the dose used in the trial for LMWH followed by aspirin varied between 81mg and 181mg per day. The nearest standard dose available in the UK is 150mg per day.<br><br>Extended duration prophylaxis was recommended in the previous guideline (CG92) for the elective total hip replacement population. The duration of prophylaxis was discussed with the following definitions considered: 10–14 days for standard and 28–35 for extended. The committee and orthopaedic subgroup noted that clinical trials and the network meta-analyses suggested possible clinical benefit of prophylaxis with an extended duration. The quality of this evidence was assessed to be very low, reporting data from comparatively few participants in a small number of trials. The estimates of the effect were consequently imprecise and the risk of bias assessed to be serious. More modern trials are conducted with extended prophylaxis strategies since this has come to be the standard-of-care despite the uncertainty around the evidence from the earlier variable duration trials conducted with LMWH.<br><br>The committee also noted that the modern practice of early mobilisation for these patients called into question whether extended duration prophylaxis is effective in current practice. The committee considered that more up-to-date evidence based in the current context is needed to evaluate the effectiveness of extended duration pharmacological prophylaxis compared to standard duration. The committee prioritised this as a key research recommendation as it represents a large population and could have potential cost savings for the NHS.<br><br>The committee noted that the single trial that represented the evidence for aspirin (standard duration) effectiveness and was included in the NMAs was old and used a non-standard dosing regimen with aspirin administered on alternate days post-operatively. The economic model showed lack of cost effectiveness, with aspirin ranking last and worse than no prophylaxis. However, the experience of the orthopaedic surgeons in the orthopaedic subgroup suggests that aspirin may be a suitable prophylaxis option for some individuals. Hence the committee suggested a |

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| | research recommendation comparing aspirin to other prophylaxis options; given its low cost aspirin could be a cost-effective option if proven to be clinically effective.<br>The committee made a high-priority research recommendation on duration of prophylaxis, and a research recommendation on aspirin, in this population group; see appendix R for more details. |

# 27 Elective knee replacement surgery

## 27.1 Introduction

Elective knee replacement surgery involves a large number of patients per year, with an increasing application in younger age groups. The general risks of this surgery, including infection, are well documented.

An objection to using pharmacological VTE prophylaxis is the increased risk of bleeding as a result of anticoagulation. The benefit of VTE prophylaxis has to be weighed against the risks and consequences of a post-operative bleed.

## 27.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective knee replacement surgery?

For full details see review protocol in appendix C.

**Table 80: PICO characteristics of review question**

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| **Population** | Adults and young people (16 years and older) undergoing elective knee replacement surgery admitted to and discharged from hospital |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion (CPM)<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) |

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| | • Vitamin K Antagonists:<br>  ○ warfarin (variable dose only)<br>  ○ acenocoumarol (all doses)<br>  ○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (2.5mg twice daily)<br>• Dabigatran (220mg once daily; 150mg once daily - patients with moderate renal impairment, interacting medicines, over 75 years old)<br>• Rivaroxaban (10mg once daily)<br>• Aspirin (up to 300mg)*<br><br>*off-label |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br>• Surgical site haematoma (up to 45 days from hospital discharge)<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study) |

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| | • Infection (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

## 27.3 Clinical evidence

Twenty-eight studies were included in this evidence review, these are summarised in Table 81 below. Fourteen studies were previously included in the previous guideline (CG92) [17,34,64,66,88,93,95,105,106,191,192,233,310,318] and fourteen studies were added in the update [4,52,53,180,188,189,216 104,252,300,330 31 186 151].

Two technology appraisals were previously included in the previous guideline; [228 229]. These technology appraisals [229]; evaluated evidence identified in the update [252 300] and evidence included in the CG92 [88 180].

Six studies that were previously included in CG92, have been excluded from this evidence review due to incorrect interventions and incorrect comparisons [125 141,144,194,209,315].

Three Cochrane reviews [139 98 261] were identified which looked at continuous passive motion, heparin and vitamin K antagonists for the prevention of venous thromboembolism people undergoing elective knee replacement. The reviews included studies which were included in the previous guideline (CG92) and this current update.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 82, Table 83, Table 84, Table 85, Table 86, Table 87, Table 88, Table 89, Table 90, Table 91, Table 92, Table 93, Table 94, Table 95, Table 96, Table 97, Table 98, Table 99, Table 100, Table 101, Table 102, Table 103, Table 104, Table 105, Table 106, Table 107, Table 108, Table 109, Table 110, Table 111, Table 112, Table 113, Table 114, Table 115, Table 116, Table 117 and Table 118). 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.

In order to input the clinical effectiveness data of multiple possible interventions into the economic model, it was proposed that a network meta-analysis be carried out on the outcome data for DVT, PE and major bleeding. For full details on the NMA methodology and results, please see appendix M.

**Table 81: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| Alkire 2010 [4] | Intervention (n=33):<br>Continuous passive motion, Danniflex 480 apparatus, used 3 times daily for 3 days.<br><br>Comparison (n=32):<br>No VTE prophylaxis<br><br>Concomitant treatment:<br>Physiotherapy given in both arms, twice daily | n=65<br><br>People undergoing elective knee replacement surgery, mean duration of surgery not reported<br><br>Age (mean): 66 years<br>Gender (male to female ratio): 1:1.46<br><br>USA | DVT (symptomatic and asymptomatic)(90 days): definition not reported | New study |
| Bauer 2001 [17] | Intervention (n=523):<br>LMWH, enoxaparin, 30mg twice daily (high dose) subcutaneously. | n=1049<br><br>People undergoing elective major knee | All-cause mortality (49 days)<br><br>DVT (symptomatic and | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | Administered postoperatively until day 5 to 9. Use of AES (length unspecified) in 81% of patients.<br><br>Comparison (n=526):<br>Fondaparinux sodium, 2.5 mg once daily orally and a placebo once daily, subcutaneously. Administered postoperatively until day 5 to 9. Use of AES (length unspecified) in 83% of patients. | replacement surgery, mean duration of surgery 128 minutes<br><br>Age (mean): 67.5 years<br>Gender (male to female ratio): 1:1.4<br><br>Multicentre, USA | asymptomatic) (49 days): confirmed by systematic bilateral ascending venography<br><br>PE (49 days): confirmed by lung scan, pulmonary angiography or helical computed tomography or at autopsy<br>Major bleeding (49 days): defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.<br><br>Fatal PE (49 days) | |
| Bern 2015[31] | Intervention (n=54)<br>Fondaparinux, 2.5mg once daily, orally from 6 or more hours (no later than 6AM the next day) postoperatively, or 6-8 hours after epidural catheter removal, continued for 28±2 days. IPCD was worn for duration on stay in hospital. AES were prescribed for use after discharge.<br><br>Comparison (n=64)<br>VKA, warfarin, dose of 5.0mg the night before surgery, followed by 5.0mg the evening of surgery, variable dose (target INR 2.0-2.5) until day 28±2 days. IPCD was worn for | n=118<br><br>People undergoing elective primary unilateral total knee replacement surgery, mean duration of surgery not reported<br><br>Age (mean): 64 years<br>Gender (male to female ratio): 1:1<br><br>USA | All-cause mortality (30 days)<br><br>DVT (symptomatic and asymptomatic) (30 days): confirmed by bilateral duplex sonography<br><br>PE (30 days): confirmed by ventilation/perfusion lung scan or computerised axial tomography angiogram | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | duration on stay in hospital. AES were prescribed for use after discharge. | | | |
| Blanchard 1999A[34] | Intervention (n=67): LMWH, nadroparin, dose adjusted to patient's body weight (<50kg, 2850 IU; 51-71kg, 3800 IU; 71-100kg, 5700 IU) (standard adjusted dose), subcutaneously administered 12 hours preoperatively then 12 hours postoperatively, once daily for 12 days<br><br>Comparison (n=63): Intermittent pneumatic compression device (IPCD), started 12 hours preoperatively, discontinued for surgery reapplied after surgery | n=130<br><br>People undergoing elective knee replacement surgery, mean duration of surgery 135 minutes<br><br>Age (mean): 73 years<br>Gender (male to female ratio): 1:3<br><br>Mean BMI in LMWH group: 43.6<br>Mean BMI in IPCD group: 44.7<br><br>Switzerland | DVT (symptomatic and asymptomatic) (8-10 days): confirmed by phlebography or venous compression ultrasonography<br><br>PE (8-10 days): definition not reported<br><br>Major bleedings (8-10 days): definition not reported | Included in CG92 |
| Chin 2009[52] | Intervention 1 (n=110): LMWH, enoxaparin, 40 mg once daily (standard dose), subcutaneously given for 5-7 days.<br><br>Intervention 2 (n=110): Intermittent pneumatic compression device (IPCD), one minute per inflation-deflation cycle with pressures ranging from 45-52mmHg, applied for 5-7 days<br><br>Intervention 3 (n=110): AES, length not specified, on both legs, applied for 5-7 days<br><br>Comparison (n=110): No prophylaxis, no | n=440<br><br>People undergoing elective total knee replacement, median duration of surgery 94 minutes<br><br>Age (mean): 66 years<br>Gender (male to female ratio): 1:9<br><br>Singapore | DVT (symptomatic and asymptomatic) (30 days): confirmed by bilateral duplex ultrasonography<br><br>PE (30 days): confirmed by ventilation-perfusion scanning and spiral computed tomography<br><br>Major bleeding (time-point not reported): major bleeding requiring intervention<br><br>Technical complications of mechanical interventions (time-point not reported): examples given were skin rash, swelling above the appliance, | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | further details reported<br><br>Concomitant treatment:<br>Standardised rehabilitation, continuous passive movements on day 2 then ambulation on day 3 | | pressure necrosis of the skin, peroneal nerve palsy<br><br>Wound infection (30 days) | |
| Cho 2013[53] | Intervention (n=74):<br>Fondaparinux, 2.5mg, once daily, subcutaneously given for 5 days. AES (length not specified) was applied also. First dose administered at 6-8 hours after the surgery, second dose given 24 hours after the first.<br><br>Comparison (n=74):<br>AES (length not specified) and placebo, 0.25ml saline once daily. First dose administered at 6-8 hours after the surgery, second dose given 24 hours after the first | n=148<br><br>People undergoing elective unilateral primary knee replacement surgery who were deemed low risk, mean duration of surgery not reported.<br><br>Age (mean): 68.5 years<br>Gender (male to female ratio): 1:11.3<br><br>South Korea | All-cause mortality (90 days)<br><br>DVT (symptomatic and asymptomatic)(7 days): confirmed by Doppler ultrasonography<br><br>PE (7 days): confirmed by ventilation perfusion lung scan and CT pulmonary angiography | New study |
| Colwell 1995D [64] | Intervention (n=228):<br>LMWH, enoxaparin, 30 mg twice daily (high dose) subcutaneously given for 14 days postoperatively. No further details reported about how long after the operation the intervention started.<br><br>Comparison (n=225):<br>Unfractionated heparin, 5000IU three times daily, subcutaneously given | n=453<br><br>People undergoing elective knee replacement surgery, mean duration of surgery not reported<br><br>Age (mean): 68 years<br>Gender (male to female ratio): 1:1.3<br><br>USA | DVT (symptomatic and asymptomatic) (15 days): confirmed by unilateral radiocontrast venography and bilateral venography<br><br>PE (15 days): confirmed by ventilation perfusion lung scan<br><br>Major bleeding (15 days): no definition reported | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | for 14 days postoperatively. No further details reported about how long after the operation the intervention started. | | | |
| Comp 2001[66] | Intervention (n=217):<br>Extended duration LMWH, enoxaparin, 30 mg twice daily (high dose) subcutaneously for 7-10 days. Patients were then administered 40mg once daily subcutaneously for 3 weeks<br><br>Comparison (n=221):<br>Standard duration LMWH, enoxaparin, 30 mg twice daily (high dose) subcutaneously for 7-10 days. Patients were then administered placebo, saline subcutaneously for 3 weeks. | n=438<br><br>People undergoing elective knee replacement surgery, duration of surgery not reported<br><br>Age (mean): 66 years<br>Gender (male to female ratio): 1:1.34<br><br>Multicentre, USA | DVT (symptomatic and asymptomatic) (27-29 days): confirmed by segment-filling defects on lower-extremity ascending contrast venograms.<br><br>PE (27-29 days): confirmed by high-probability ventilation-perfusion lung scan or pulmonary angiogram<br><br>Major bleeding (27-29 days): defined as clinically overt and resulted in death, transfusion of two or more units of blood products, a decrease in haemoglobin level of ≥2.0 g/dL (≥20 g/L) compared with the most recent preceding postoperative value, or a serious or life-threatening clinical event or one requiring surgical intervention or if it was retroperitoneal, intracranial, or intraocular in location.<br><br>Heparin-induced thrombocytopaenia (27-29 days) | Included in CG92 |
| Eriksson 2007: RE-MODEL trial[88] | Intervention (n=699):<br>LMWH, enoxaparin, 40mg, once daily (standard dose), subcutaneously given, administered from the evening before surgery, treatment was | n=1393<br><br>People undergoing elective primary unilateral total knee replacement, mean duration of surgery | All-cause mortality (13 days)<br><br>DVT (symptomatic and asymptomatic) (13 days): confirmed by bilateral venography | Included in CG92<br><br>Third arm of this trial evaluated use of a |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | continued for 6-10 days. Patients received two capsules (placebo) in the morning and a daily subcutaneous injection in the evening.<br><br><u>Comparison (n=694):</u><br>Dabigatran, 220mg, once daily, orally. First dose was one-half (110mg) and was administered 1-4 hours after completion of surgery. Treatment was continued for 6-10 days. Patients received two capsules in the morning and a daily subcutaneous injection (placebo) in the evening.<br><br><u>Concomitant treatment:</u><br>AES was permitted, no further details reported about the percentage of patients who used AES | 91 minutes<br><br>Age (mean): 68 years<br>Gender (female to male): 1:1.8<br><br>Multicentre, 105 centres in Europe, Australia and South Africa | PE (13 days): confirmed by ventilation/perfusion scintigraphy, pulmonary angiography, spiral computed tomography, or autopsy<br><br>Fatal PE (13 days): confirmed by ventilation/perfusion scintigraphy, pulmonary angiography, spiral computed tomography, or autopsy<br><br>Major bleeding (13 days): defined as fatal bleeding; clinically overt bleeding associated with a decrease in the haemoglobin level of more than 20 g/l compared with the pre-randomisation level; clinically overt bleeding leading to transfusion of two or more units of whole blood or packed cells; critical bleeding (intracerebral, intraocular, intraspinal, pericardial or retroperitoneal); bleeding warranting treatment cessation; bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (e.g. draining or puncture of an haematoma at the surgical site, transfer to an ICU or | different dose of dabigatran (150mg/day)<br><br>NICE Technology Appraisal TA157 2008 [228] |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | | | emergency room)<br><br>Clinically relevant non-major bleeding (13 days): defined as any clinically overt bleeding that does not meet the criteria for major bleeding but requires medical attention (e.g.: hospitalisation, medical treatment for bleeding) and/or a change in antithrombotic therapy (including discontinuation or downtitration of study drug) and/or any other bleeding type considered to have clinical consequences for a patient | |
| Fauno 1994 [93] | Intervention (n=92):<br>LMWH, enoxaparin, 40mg once daily (standard dose) subcutaneously. Administered from the evening before the operation, and continued for 7-10 days. AES, short, on the operated limb and long AES on the contralateral limb.<br><br>Comparison (n=93):<br>Unfractionated heparin (UFH), 5000IU three times daily, subcutaneously. Administered from the evening before the operation, and continued for 7-10 days. AES, short, on the operated limb and long AES on the contralateral limb. | n=185<br><br>People undergoing elective primary knee replacement surgery, mean duration of surgery 103 minutes<br><br>Age (mean): 71 years<br>Gender (male to female ratio): 1:1.5<br><br>Denmark | DVT (symptomatic and asymptomatic) (7-9 days): confirmed by bilateral ascending venography<br><br>PE (7-9 days): confirmed by ventilation-perfusion lung scintigraphy<br>Wound haematoma (7-9 days)<br><br>Wound infection (7-9 days) | Included in CG92 |
| Fitzgerald 2001[95] | Intervention (n=173):<br>LMWH, enoxaparin, 30mg twice daily (high | n=349<br><br>People undergoing | All-cause mortality (15 days) | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | dose) subcutaneously. Intervention began on the day of surgery, was continued for 4-14 days.<br><br>Comparison (n=176):<br>Warfarin, initial dose of 7.5mg, followed by daily adjustment of dose to maintain INR of 2-3. Intervention began on the day of surgery, was continued for 4-14 days.<br><br>Concomitant treatment:<br>Use of AES was permitted, no further details about percentage of people who received AES | elective primary total knee replacement, mean duration of surgery not reported<br><br>Age (mean): not reported<br>Gender (male to female ratio): 1:1.3<br><br>Multicentre, USA | DVT (symptomatic and asymptomatic) (15 days): confirmed by bilateral lower-extremity ultrasonography, unilateral venography.<br><br>PE (15 days): confirmed by high-probability ventilation-perfusion lung scan or a positive pulmonary angiogram<br><br>Major bleeding (15 days): defined as major if it fulfilled at least one of the following criteria: resulted in transfusion of at least two units of packed red blood cells; resulted in a decrease in the haemoglobin concentration of ≥20 g/L compared with the postoperative haemoglobin concentration before the administration of any study medication; was retroperitoneal, intracranial, or intraocular; or resulted in a serious life-threatening clinical event or death | |
| Fuji 2008[105] | Intervention (n=84):<br>Fondaparinux, 2.5mg subcutaneously once daily. Administered 24±2 hours after surgery until 10-16 days. More than 50% received AES.<br><br>Comparison (n=87):<br>More than 50% received AES. Placebo, 0.25ml isotonic sodium chloride, subcutaneously once | n=171<br><br>People undergoing elective knee replacement surgery,<br><br>Age (mean): 61.6 years<br>Gender (male to female ratio):4.6:1<br><br>Japan | All-cause mortality (11-17 days)<br><br>Major bleeding (11-17 days): defined as fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with bleeding index of 2 or more. | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | daily. Administered 24±2 hours after surgery until 10-16 days. | | | |
| Fuji 2008A[106] | Intervention 1 (n=78): LMWH, enoxaparin, 20mg (low dose), subcutaneously once daily, administered 24-36 hours after surgery for 14 days. More than 50% received AES<br><br>Intervention 2 (n=74): LMWH, enoxaparin, 40mg (standard dose) once daily, administered 24-36 hours after surgery for 14 days.<br><br>Comparison (n=79): Placebo (saline). Administered 24-36 hours after surgery for 14 days. More than 50% received AES | n=231<br><br>People undergoing elective knee replacement surgery, duration of surgery not reported<br><br>Age (mean): 69 years<br>Gender (male to female ratio): 1:5<br><br>Japan | DVT (symptomatic and asymptomatic) (14 days): confirmed by Doppler ultrasound<br><br>PE (90 days): confirmed by ventilation perfusion lung scans or pulmonary angiography<br><br>Major bleeding (15 days): retroperitoneal, intracranial, or intraocular or if it was associated with: death; transfusion of ≥2 units of packed red blood cells or whole blood (except autologous); a reduction in the haemoglobin level of ≥2 g/dl; or a serious or life-threatening clinical event that required medical intervention. | Included in CG92 |
| Fuji 2010[104] | Intervention (n=129): Dabigatran, 220mg, once daily, orally given from 'as early as possible' or at least 2 hours after removing the indwelling catheter and confirming the absence of abnormal bleeding from the drainage sites for 11-14 days. Patients received two capsules per day.<br><br>Comparison (n=124): Placebo, no prophylaxis, orally given from 'as early as | n=253<br><br>People undergoing elective primary unilateral knee replacement surgery, mean duration of surgery 109 minutes<br><br>Age (mean): 72 years<br>Gender (male to female ratio): 1:1.6<br><br>Japan | All-cause mortality (14 days)<br><br>DVT (symptomatic and asymptomatic) (14 days): confirmed by bilateral venography<br><br>PE (14 days): confirmed by pulmonary scintigraphy, pulmonary angiography, or contrast computed tomography<br><br>Major bleeding (14 days): defined as a | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | possible' or at least 2 hours after removing the indwelling catheter and confirming the absence of abnormal bleeding from the drainage sites for 11-14 days. Patients received two capsules per day.<br><br><u>Concomitant treatment:</u><br>AES permitted (percentage of patients who received AES not reported). | | bleeding event that meets at least one of the following criteria: fatal bleeding, critical bleeding (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, in a non-operated joint, or intramuscular with compartment syndrome), clinically overt bleeding (at surgical or extrasurgical site) associated with a decrease in the haemoglobin level of more than 2 g/dL (20 g/l; 1.24 mmol/L) compared with the pre-randomisation level, clinically overt bleeding (at surgical or extrasurgical site) leading to transfusion of two or more units of whole blood or packed cells, bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (e.g. draining or puncture of an haematoma at the surgical site, transfer to an ICU or emergency room)<br><br>Clinically relevant non-major bleeding (14 days): defined as any clinically overt bleeding that does not meet the criteria for major bleeding but requires medical attention (e.g.: hospitalisation, medical treatment for bleeding) and/or a change in antithrombotic therapy | |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | (including discontinuation or down-titration of study drug) and/or any other bleeding type considered to have clinical consequences for a patient. | |
| Ginsberg 2009: RE-MOBILIIZE trial [252] | Intervention (n=876): LMWH, enoxaparin, 30mg twice daily (high dose), subcutaneously given12-24 hours after surgery for 12-15 days. Two placebo tablets given in the morning.<br><br>Comparison (n=862): Dabigatran, 110mg, 6-12 hours after surgery then 220mg once daily (standard dose) for 12-15 days. Placebo subcutaneously given also. | n=1738<br><br>People undergoing elective primary unilateral knee replacement surgery, mean duration of surgery 91 minutes<br><br>Age (mean): 66 years<br>Gender (male to female ratio): 1:1.38<br><br>Multicentre | All-cause mortality (18 days)<br><br>DVT (symptomatic and asymptomatic) (18 days): confirmed by bilateral venography<br><br>PE (18 days): confirmed by high-probability result on ventilation-perfusion scintigraphy, pulmonary angiography, spiral computed tomography or autopsy.<br><br>Major bleeding (18 days): defined as a bleeding event that meets at least one of the following criteria: fatal bleeding, critical bleeding (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, in a non-operated joint, or intramuscular with compartment syndrome), clinically overt bleeding (at surgical or extrasurgical site) associated with a decrease in the haemoglobin level of more than 2 g/dL (20 g/l; 1.24 mmol/L) compared with the pre-randomisation level, clinically overt bleeding (at surgical or extrasurgical site) leading to transfusion | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | of two or more units of whole blood or packed cells, bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (e.g. draining or puncture of an haematoma at the surgical site, transfer to an ICU or emergency room)<br><br>Fatal PE (18 days): confirmed by autopsy<br><br>Clinically relevant non-major bleeding (18 days): defined as any clinically overt bleeding that does not meet the criteria for major bleeding but requires medical attention (e.g.: hospitalisation, medical treatment for bleeding) and/or a change in antithrombotic therapy (including discontinuation or down-titration of study drug) and/or any other bleeding type considered to have clinical consequences for a patient. | |
| Intiyanaravut 2017 [151] | <u>Intervention (n=25):</u><br>LMWH, enoxaparin, 40mg, once daily (standard dose), subcutaneously given from 24 hours post-operation and continued for 10 days. Continuous passive motion was initiated on second day post-operation. | n=50<br><br>People undergoing elective primary knee replacement surgery, mean duration of surgery 130 minutes<br><br>Age (mean): 71 years<br>Gender (male to female ratio): 1:5 | DVT (symptomatic and asymptomatic) (6-10 days): confirmed by bilateral colour Doppler ultrasonography<br><br>PE (time-point not reported): confirmed by clinical signs scoring system (sudden dyspnoea, chest pain and cough of | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison (n=25):<br>No prophylaxis. Continuous passive motion was initiated on second day post-operation.<br><br>Concomitant treatment:<br>Compression dressing was used in the first 24 hours. Active mobilisation and full weight-bearing ambulation was initiated. | Thailand | haemoptysis)<br><br>Major bleeding (time-point not reported): defined as the presence of grade three haematoma which requiring operative removal and bleeding that was fatal or involved a critical organ. | |
| Lassen 2007: APROPOS trial | Intervention 1 (n=152):<br>LMWH, enoxaparin, 30mg twice daily (high dose), subcutaneously given every 12 hours, began 12-24 hours postoperatively continued for 12±2 days. Placebo tablets also given.<br><br>Intervention 2 (n=310)<br>Apixaban, 2.5mg twice daily or 5mg once daily orally, began 12-24 hours postoperatively continued for 12±2 days. Placebo injections also given.<br><br>Comparison (n=153)<br>VKA, warfarin, orally given once daily, loading dose of 5mg (two 2.5mg tablets), then adjusted dose to maintain INR in the range of 1.8-3.0, from the evening of the day of surgery continued for 12±2 days. | n=615<br><br>People undergoing elective total knee replacement, mean duration of surgery 90 minutes<br><br>Age (mean): 68 years<br>Gender (male to female ratio): 1:1.7<br><br>97 centres in Argentina, Australia, Canada, Mexico, Denmark, Israel, Poland, USA | All-cause mortality (12±2 days)<br><br>DVT (symptomatic and asymptomatic) (12±2 days): confirmed by bilateral ascending venogram<br><br>PE (12±2 days): confirmed by computed tomography (CT), pulmonary angiography or a ventilation-perfusion lung scan.<br><br>Major bleeding (12±2 days): defined as overt bleeding accompanied by a reduction in haemoglobin of ≥2 g $dL^{-1}$ (relative to the postsurgical value) and/or a requirement for transfusion of ≥2 units of blood product, or a need to discontinue study medication, or if it was intracranial or intraspinal, retroperitoneal, or in the operated joint necessitating re-operation or intervention, intrapericardial, | Pre-CG92 not included<br><br>Two arms of apixaban doses combined (2.5mg twice daily and 5mg once daily) to reflect BNF approved dose |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | intraocular or fatal.<br><br>Fatal PE (12±2 days): defined by autopsy<br><br>Wound infections (12±2 days) | |
| Lassen 2008: RECORD-3 trial [180] | Intervention (n=1277):<br>LMWH, enoxaparin, 40mg once daily (standard dose), subcutaneously given 12 hours before surgery then 6-8 hours after wound closure, administered for 10-14 days. Placebo oral tablet was also given.<br><br>Comparison (n=1254):<br>Rivaroxaban, 10mg, once daily, initiated 6-9 hours after closure, administered every 24 hours for 10-14 days. Placebo injection was also given. | n=2459<br><br>People undergoing elective knee replacement, mean duration of surgery 97 minutes<br><br>Age (mean): 67.6 years<br>Gender (male to female ratio): 1:2.1<br><br>Multicentre – Austria, Belgium, Canada, China, Colombia, Czech Republic, Denmark Germany, France, Israel, Italy, the Netherlands, Mexico, Norway, Poland, Peru, South Africa, Spain and Sweden | All-cause mortality (35 days)<br><br>DVT (symptomatic and asymptomatic) (17 days): confirmed by ascending bilateral venography<br><br>PE (17 days): confirmed by ventilation-perfusion scintigraphy of the lung and chest radiography or spiral computed tomography, or pulmonary angiography.<br><br>Major bleeding (17 days): defined as bleeding that was fatal, that involved a critical organ, or that required reoperation or clinically overt bleeding outside the surgical site that was associated with a decrease in the haemoglobin level of 2 g or more per decilitre or requiring infusion of 2 or more units of blood.<br><br>Clinically relevant non-major bleeding (17 days): definition not reported<br><br>Wound infection (17 days) | New study<br><br>NICE Technology Appraisal TA170 2009 [229] |
| Lassen 2009: ADVANCE-1 | Intervention (n=1596):<br>LMWH, enoxaparin, | n=3195 | All-cause mortality (60 days) | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| trial [189] | 30mg every 12 hours (high dose), subcutaneously given from 12-24 hours post-surgery. Intervention administered from 10-14 days. Placebo apixaban tablets also given.<br><br><u>Comparison (n=1599):</u><br>Apixaban, 2.5mg twice daily, orally given from 12-24 hours post-surgery. Intervention administered from 10-14 days. Placebo enoxaparin, subcutaneously given also. | People undergoing elective total knee replacement surgery, mean duration of surgery 114 minutes<br><br>Age (median): 65.8 years<br>Gender (male to female ratio): 1:1.64<br><br>Multicentre – North America, Europe, Latin America, Asia and Pacific Islands | DVT (symptomatic and asymptomatic) (14 days): confirmed by ascending bilateral venography<br><br>PE (14 days): confirmed by ventilation–perfusion scintigraphy of the lung and chest radiography or spiral computed tomography were performed, or pulmonary angiography was performed<br><br>Major bleeding (14 days): defined as bleeding that was fatal, that involved a critical organ, or that required reoperation or clinically overt bleeding outside the surgical site that was associated with a decrease in the haemoglobin level of 2 g or more per decilitre or requiring infusion of 2 or more units of blood.<br><br>Fatal PE (14 days): confirmed by autopsy<br><br>Clinically relevant non-major bleeding (14 days): such bleeding included acute, clinically overt bleeding, such as wound hematoma, bruising or ecchymosis, Gastrointestinal bleeding, haemoptysis, haematuria, or epistaxis that did not meet the other criteria for major bleeding. | |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | Wound haematoma (14 days) | |
| Lassen 2010: ADVANCE-2 trial[188] | Intervention (n=1529): LMWH, enoxaparin, 40mg once daily (standard dose), subcutaneously given12 hours before operation then resumed after surgery. Intervention administered for 10-14 days, placebo apixaban tablets given also.<br><br>Comparison (n=1528): Apixaban, 2.5mg twice daily, orally from 12-24 hours after wound closure. Intervention administered for 10-14 days, subcutaneous placebo injections of enoxaparin. | n=3057<br><br>People undergoing elective total knee replacement surgery, mean duration of surgery 118 minutes<br><br>Age (median): 67 years<br>Gender (male to female ratio): 2.63:1<br><br>Multicentre – Europe, Asia/Pacific, Latin America, South Africa | All-cause mortality (60 days)<br><br>DVT (symptomatic and asymptomatic)(14 days): confirmed by ascending bilateral venography<br><br>PE (60 days): confirmed by ventilation–perfusion scintigraphy of the lung and chest radiography or spiral computed tomography were performed, or pulmonary angiography was performed<br><br>Major bleeding (14 days): defined as bleeding that was fatal, that involved a critical organ, or that required reoperation or clinically overt bleeding outside the surgical site that was associated with a decrease in the haemoglobin level of 2 g or more per decilitre or requiring infusion of 2 or more units of blood.<br><br>Fatal PE: confirmed by autopsy<br><br>Clinically relevant non-major bleeding (14 days): such bleeding included acute, clinically overt bleeding, such as wound hematoma, bruising or ecchymosis, Gastrointestinal | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | bleeding, haemoptysis, haematuria, or epistaxis that did not meet the other criteria for major bleeding<br><br>Wound haematoma (14 days) | |
| Leclerc 1992 [191] | Intervention (n=66):<br>LMWH, enoxaparin, 30mg twice daily (high dose), subcutaneously given from the morning of the first post-operative day and was continued for 14 days or until discharge if sooner.<br><br>Comparison (n=65):<br>Placebo, saline, 0.4ml saline twice daily | n=131<br><br>People undergoing elective knee replacement surgery or tibial osteotomy, mean duration of surgery 145 minutes<br><br>Age (mean): 69 years<br>Gender (male to female ratio):1:1.5<br><br>Canada | All-cause mortality (14 days)<br><br>DVT (symptomatic and asymptomatic) (14 days): confirmed by bilateral contrast venography<br><br>Major bleeding (14 days): defined by a drop in haemoglobin of 20 g/l or more, requiring transfusion with two or more units of packed red cells or occurring in any of these site: intracranial, intra-ocular, retroperitoneal space or intra-articular. | Included in CG92 |
| Leclerc 1996 [192] | Intervention (n=336):<br>LMWH, enoxaparin, 30mg twice daily (high dose) subcutaneously administered on the morning of the first day after surgery. Administered for 14 days or until hospital discharge, whichever occurred first. Patients also received warfarin placebo once daily from the evening of the operation.<br><br>Comparison (n=334):<br>Warfarin, initial dose not reported, treatment goal was to maintain the INR 2-3. Administered from the evening of the | n=670<br><br>People undergoing elective knee replacement surgery, mean duration of surgery 125 minutes<br><br>Age (mean): 69 years<br>Gender (male to female ratio): 1:1.7<br><br>Multicentre, USA | All-cause mortality (14 days)<br><br>DVT (symptomatic and asymptomatic) (14 days): confirmed by venography<br><br>PE (14 days): confirmed by perfusion scan and high-probability scan<br><br>Major bleeding (14 days): defined as overt bleeding that decreased the haemoglobin level by 20 g/L r more or necessitated transfusion of 2 or more units of packed red cells, | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | operation for 14 days or until hospital discharge, whichever occurred first. Patients also received subcutaneous saline placebo twice daily (every 12 hours) | | haemarthrosis requiring evacuation, discontinuation of prophylaxis, or interruption of physiotherapy for at least 24 hours.<br><br>Wound haematomas (14 days) | |
| Mirdamidi 2014 [216] | Intervention (n=45):<br>LMWH, enoxaparin, 40mg once daily (standard dose), subcutaneously given from 12 hours before surgery and continued for up to 15 days.<br><br>Comparison (n=45):<br>Dabigatran, 150mg, 4 hours after surgery and continued daily at an increased dose of 225mg for up to 15 days. | n=90<br><br>People undergoing elective primary total knee replacement, mean duration of surgery not reported<br><br>Age (mean): 70 years<br>Gender (male to female ratio): 1:1.37<br><br>Iran | All-cause mortality (15 days)<br><br>PE (15 days): confirmed by ventilation/perfusion scintigraphy, spiral computed tomography<br><br>Major bleeding (15 days): defined as clinically overt bleeding associated with ≥ 20 g/l fall in haemoglobin; clinically overt bleeding leading to a transfusion of ≥ 2 units of packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding and bleeding warranting treatment cessation or leading to reoperation.<br><br>Clinically relevant non-major bleeding (15 days): defined as bleeding that included spontaneous hematoma ≥ 25 cm3, wound hematoma ≥ 100 cm3, epistaxis > 5 min, spontaneous haematuria or a prolonged one after intervention, spontaneous rectal bleeding, gingival bleeding > 5 min | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Norgren 1998 [233] | Intervention (n=19): LMWH, enoxaparin, 40mg once daily (standard dose) subcutaneously. No details reported about when first dose was administered. Intervention continued until full mobilisation, further details not reported.<br><br>Comparison (n=21): Foot pump, plus AES. Started evening before surgery, reapplied immediately after and continued until full mobilisation. A tourniquet was used during surgery. | n=40<br><br>People undergoing elective knee replacement surgery, duration of surgery not reported<br><br>Age (mean): 72 years<br>Gender (male to female ratio): 1:1.6<br><br>Country not reported | DVT (symptomatic and asymptomatic)(7-10 days): confirmed by venography<br><br>Fatal PE (90 days): confirmed by autopsy | Included in CG92<br><br>11 patients dropped out of the study, 5 in the LMWH group and 6 in the foot pump group |
| Turpie 2009: RECORD-4 trial [300] | Intervention (n=1564): LMWH, enoxaparin, 30mg twice daily (high dose), subcutaneously given from 12-24 hours after wound closure for 11-15 days. Placebo rivaroxaban oral tablets given also.<br><br>Comparison (n=1584): Rivaroxaban, 10mg, orally once daily, from 6-8 hours after wound closure for 11-15 days. Placebo enoxaparin subcutaneously injections given also. | n=3148<br><br>People undergoing elective total knee replacement, mean duration of surgery 100 minutes<br><br>Age (mean): 65 years<br>Gender (male to female ratio):1:1.86<br><br>Canada, USA | All-cause mortality (35 days)<br><br>DVT (symptomatic and asymptomatic) (17 days): confirmed by venography<br><br>PE (17 days): confirmed by pulmonary angiography, by ventilation-perfusion lung scintigraphy with chest radiography, or by contrast-enhanced spiral CT.<br><br>Major bleeding (17 days): defined as defined as bleeding that was fatal, that involved a critical organ, or that required reoperation or clinically overt bleeding outside the surgical site that was associated with a decrease in the haemoglobin level of 2 g or more per decilitre | New study<br><br>NICE Technology Appraisal TA170 2009 [229] |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | or requiring infusion of 2 or more units of blood.<br><br>Fatal PE (17 days): confirmed by pulmonary angiography, by ventilation-perfusion lung scintigraphy with chest radiography, or by contrast-enhanced spiral CT.<br><br>Clinically relevant non-major bleeding (17 days): defined as multiple-source bleeding, unexpected haematoma (>25 cm2), excessive wound haematoma, nose bleeding, gingival (>5 minutes), macroscopic haematuria, rectal bleeding, coughing or vomiting blood, vaginal bleeding, blood in semen, intra-articular bleeding with trauma, or surgical-site bleeding<br><br>Wound infection (time-point not reported) | |
| Warwick 2002 [310] | Intervention (n=112):<br>LMWH, enoxaparin 40mg once daily (standard dose), subcutaneously, administered from 12 hours before surgery and every 24 hours thereafter until discharge from hospital.<br>AES fitted below the knee before surgery, stocking on operated side was removed for duration of surgery and for some time after, no further details reported about length | n=229<br><br>People undergoing elective total knee replacement, mean duration of surgery not reported<br><br>Age (mean): 72 years<br>Gender (male to female ratio): 1:1.9<br><br>UK | DVT (symptomatic and asymptomatic) (8 days): confirmed by ascending venography<br><br>Fatal PE (time-point not reported): definition not reported<br><br>Wound haematomas (time-point not reported) | Included in CG92 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | of time AES worn for.<br><br><u>Comparison (n=117):</u><br>Foot pump, pressure of 130mmHg applied for one second, every 20 seconds. Foot pump applied in the recovery room, controller was engaged, foot pump used whenever patients was not weight-bearing until discharge from hospital. AES fitted below the knee before surgery, stocking on operated side was removed for duration of surgery and for some time after, no further details reported about length of time AES worn for. | | | |
| Wilson 1992 [318] | <u>Intervention (n=28):</u><br>Foot pump, A-V Impulse System, compressor rapidly inflates the pad (0.4 seconds), deflates after a period of 3 seconds, cycle repeated every 20 seconds. Foot pump was applied to operated limb on completion of surgery.<br><br><u>Comparison (n=32):</u><br>No VTE prophylaxis, no further details reported. | n=60<br><br>People undergoing elective total knee replacements, mean duration of surgery 136 minutes<br><br>Age (mean): 71 years<br>Gender (male to female ratio): 1:3<br><br>UK | DVT (symptomatic and asymptomatic) (10 days): confirmed by ascending ipsilateral venography<br><br>PE (time-point not reported): confirmed by ventilation perfusion lung scanning | Included in CG92 |
| Zou 2014[330] | <u>Intervention 1 (n=112):</u><br>LMWH, enoxaparin, 4000IU (0.4ml)/40mg once daily (standard dose) subcutaneously given. Administered from 12 hours after the operation and continued for 14 days. | n=324<br><br>People undergoing elective unilateral total knee replacement, mean duration surgery 87 minutes | DVT (symptomatic and asymptomatic) (28 days): confirmed by colour Doppler ultrasonography<br><br>PE (time-point not reported): definition not reported | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Intervention 2 (n=102):<br>Rivaroxaban, 10mg, once daily, subcutaneously given. Administered from 12 hours after the operation and continued for 14 days.<br><br>Comparison (n=110):<br>Aspirin, 100mg, once daily, subcutaneously given. Administered from 12 hours after the operation and continued for 14 days.<br><br>Concomitant treatment:<br>Mobilisation started 1 day after surgery, they practiced walking with walking aids two or three times a day 2 days after surgery for 10-20 minutes each time. | Age (mean): 64 years<br>Gender (male to female ratio): 1:2.7<br><br>China | | |

**Table 82: 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 (standard dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 220 (1 studies) 30 days | MODERATE[a] due to risk of bias | RR 0.25 (0.11 to 0.59) | 218 per 1000 | 164 fewer per 1000 (from 89 fewer to 194 fewer) |
| PE | 220 (1 studies) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.14 (0.00 to 6.82) | 9 per 1000 | 8 fewer more per 1000 (from 9 fewer to 50 more) |
| Major bleeding | 530 (3 studies) 30 days | VERY LOW[a,b,d,f] due to risk of bias, indirectness, imprecision, inconsistency | Peto OR 0.98 (0.24 to 3.95) | 15 per 1000 | 0 fewer per 1000 (from 12 fewer to 42 more) |
| Wound haematoma | 219 (1 study) 8 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.67 (0.48 to 123.42) | 0 per 1000 | -[d] |
| Technical complications of mechanical interventions | 220 (1 study) time-point not reported | VERY LOW[a,b,d] due to risk of bias, indirectness imprecision | Not estimable[e] | Not estimable[e] | 0 fewer per 1000 (from 20 fewer to 20 more)[e] |
| Wound infection | 220 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.13 (0.01 to 2.16) | 18 per 1000 | 16 fewer per 1000 (from 18 fewer to 20 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.

| 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 (standard dose) (95% CI) |

c Absolute effects could not be calculated due to zero events in the control arm

d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

e Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

f Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.

**Table 83: 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 (standard dose) (95% CI) |
| All-cause mortality | 3057 (1 study) 60 days | LOW[a] due to imprecision | Peto OR 0.37 (0.05 to 2.61) | 2 per 1000 | 1 fewer per 1000 (from 2 fewer to 3 more) |
| DVT (symptomatic and asymptomatic) | 1968 (1 study) 14 days | MODERATE[b] due to risk of bias | RR 1.67 (1.38 to 2.01) | 146 per 1000 | 98 more per 1000 (from 56 more to 148 more) |
| PE | 3057 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.17 (0.02 to 1.38) | 4 per 1000 | 3 fewer per 1000 (from 4 fewer to 1 more) |
| Major bleeding | 3009 (1 study) 14 days | LOW[a] due to imprecision | RR 1.55 (0.67 to 3.57) | 6 per 1000 | 3 more per 1000 (from 2 fewer to 15 more) |
| Fatal PE | 3057 (1 study) 14 days | LOW[a] due to imprecision | Peto OR 0.14 (0 to 6.82) | 1 per 1000 | 1 fewer per 1000 (from 1 fewer to 4 more) |
| Clinically relevant non-major bleeding | 3009 (1 study) 14 days | MODERATE[a] due to imprecision | RR 1.31 (0.89 to 1.93) | 29 per 1000 | 9 more per 1000 (from 3 fewer to 27 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 (standard dose) (95% CI) |
| Wound haematoma | 3009<br>(1 study)<br>14 days | LOW[a]<br>due to imprecision | Peto OR 0.13<br>(0 to 6.79) | 1 per 1000 | 1 fewer per 1000<br>(from 1 fewer to 4 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 84: Clinical evidence summary: LMWH (standard dose; standard duration) versus dabigatran**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Dabigatran | Risk difference with LMWH (standard dose) (95% CI) |
| All-cause mortality | 1450<br>(2 studies)<br>13 days | LOW[b]<br>due to imprecision | Peto OR 1.01<br>(0.06 to 16.24) | 1 per 1000 | 0 more per 1000<br>(from 1 fewer to 20 more) |
| DVT (symptomatic and asymptomatic) | 1360<br>(1 study)<br>13 days | HIGH | RR 1.04<br>(0.87 to 1.24) | 270 per 1000 | 11 more per 1000<br>(from 35 fewer to 65 more) |
| PE | 1450<br>(2 studies)<br>13 days | LOW[b]<br>due to imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000<br>(from 0 fewer to 0 more)[a] |
| Major bleeding | 1463<br>(2 studies)<br>13 days | LOW[b]<br>due to imprecision | RR 0.83<br>(0.38 to 1.84) | 18 per 1000 | 3 fewer per 1000<br>(from 11 fewer to 15 more) |
| Fatal PE | 1360<br>(1 study)<br>13 days | LOW[b]<br>due to imprecision | Peto OR 7.28<br>(0.14 to 367.03) | 0 per 1000 | -[c] |
| Clinically relevant non-major bleeding | 1463 | LOW[b] | RR 0.9 | 66 per 1000 | 7 fewer per 1000 |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Dabigatran | Risk difference with LMWH (standard dose) (95% CI) |
| | (2 studies)<br>13 days | due to imprecision | (0.61 to 1.33) | | (from 26 fewer to 22 more) |

a Zero events in both arms of studies included. Risk difference calculated in Review Manager.
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 the control

**Table 85: Clinical evidence summary: LMWH (standard dose; standard duration) versus rivaroxaban**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Rivaroxaban | Risk difference with LMWH (standard dose) (95% CI) |
| All-cause mortality | 2418<br>(1 study)<br>35 days | LOW[b,c]<br>due to risk of bias, imprecision | Peto OR 7.31<br>(1.03 to 51.96) | 0 per 1000 | -[a] |
| DVT (symptomatic and asymptomatic) | 1916<br>(2 studies)<br>28 days | MODERATE[b]<br>due to risk of bias | RR 1.99<br>(1.55 to 2.54) | 89 per 1000 | 88 more per 1000<br>(from 49 more to 136 more) |
| PE | 2632<br>(2 studies)<br>17 days | LOW[b,c]<br>due to risk of bias, imprecision | Peto OR 7.31<br>(1.03 to 51.96) | 0 per 1000 | -[a] |
| Major bleeding | 2531<br>(1 study)<br>17 days | LOW[c]<br>due to imprecision | RR 0.79<br>(0.42 to 1.50) | 17 per 1000 | 4 fewer per 1000<br>(from 10 fewer to 8 more) |
| Clinically relevant non-major bleeding | 2459<br>(1 study)<br>35 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | RR 0.84<br>(0.51 to 1.37) | 27 per 1000 | 4 fewer per 1000<br>(from 13 fewer to 10 more) |
| Wound infection | 2459<br>(1 study) | VERY LOW[b,c]<br>due to risk of bias, | RR 1.55<br>(0.6 to 3.98) | 6 per 1000 | 3 more per 1000<br>(from 2 fewer to 17 more) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Rivaroxaban | Risk difference with LMWH (standard dose) (95% CI) |
| | 17 days | imprecision | | | |

a Absolute effects could not be calculated due to zero events in the control arm
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 86: 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 (standard dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 222<br>(1 study)<br>28 days | VERY LOW[a,c]<br>due to risk of bias, imprecision | RR 0.76<br>(0.4 to 1.46) | 164 per 1000 | 39 fewer per 1000<br>(from 98 fewer to 75 more) |
| PE | 222<br>(1 study)<br>28 days | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(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 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 Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

**Table 87: Clinical evidence summary: LMWH (standard dose; standard duration) 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 (standard dose) (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 (standard dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 220<br>(1 study)<br>30 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.43<br>(0.17 to 1.07) | 127 per 1000 | 73 fewer per 1000<br>(from 106 fewer to 9 more) |
| PE | 220<br>(1 study)<br>30 days) | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.14 (0.00 to 6.82) | 9 per 1000 | 8 fewer per 1000<br>(from 9 fewer to 50 more) |
| Technical complications of mechanical interventions | 220<br>(1 study)<br>time-point not reported | VERY LOW[a,b,d]<br>due to risk of bias, indirectness imprecision | Not estimable[e] | Not estimable[e] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[e] |
| Wound infection | 220<br>(1 study)<br>30 days) | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.13 (0.01 to 2.16) | 18 per 1000 | 16 fewer per 1000<br>(from 18 fewer to 20 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 Absolute effects could not be calculated due to zero events in the control arm

d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

e Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

**Table 88: Clinical evidence summary: LMWH (standard dose; standard duration) versus IPCD**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with IPCD | Risk difference with LMWH (standard dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 350<br>(2 studies)<br>30 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.49<br>(0.32 to 0.76) | 249 per 1000 | 127 fewer per 1000<br>(from 60 fewer to 169 fewer) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with IPCD | Risk difference with LMWH (standard dose) (95% CI) |
| | | | | | |
| PE | 350<br>(2 studies)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[c] |
| Technical complications of mechanical interventions | 220<br>(1 study)<br>time-point not reported | VERY LOW[a,b,d]<br>due to risk of bias, indirectness imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[e] |
| Wound infection | 220<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.14<br>(0.00 to 6.82) | 9 per 1000 | 8 fewer per 1000<br>(from 9 fewer to 50 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 Zero events in both arms. Risk difference calculated in Review Manager.
d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
e Absolute effects could not be calculated due to zero events in the control arm

**Table 89: Clinical evidence summary: LMWH (standard dose; standard duration) versus foot pump + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Foot pump + AES | Risk difference with LMWH (standard dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 29<br>(1 study)<br>10 days | LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.11<br>(0.01 to 0.91) | 267 per 1000 | 228 fewer per 1000<br>(from 18 fewer to 263 fewer) |
| Fatal PE | 29<br>(1 study) | VERY LOW[a,b,c]<br>due to risk of bias, | Peto OR 0.14<br>(0 to 7.31) | 67 per 1000 | 57 fewer per 1000<br>(from 67 fewer to 276 more) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Foot pump + AES | Risk difference with LMWH (standard dose) (95% CI) |
| | time-point not reported | indirectness, imprecision | | | |

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

**Table 90: Clinical evidence summary: LMWH (standard dose; standard duration) + AES versus foot pump + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Foot pump + AES | Risk difference with LMWH (standard dose) + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 188 (1 study) 8 days | LOW[a,b] due to risk of bias, imprecision | RR 0.94 (0.73 to 1.21) | 576 per 1000 | 35 fewer per 1000 (from 155 fewer to 121 more) |
| Fatal PE | 188 (1 study) 8 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Peto OR 0.15 (0.01 to 2.40) | 20 per 1000 | 17 fewer per 1000 (from 20 fewer to 27 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 if the outcome definition reported did not meet definition of outcome in protocol
d Absolute effects could not be calculated due to zero events in the control arm

**Table 91: Clinical evidence summary: LMWH (standard dose; standard duration) versus UFH**

| Outcomes | No of | Quality of the evidence | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | effect (95% CI) | Risk with UFH | Risk difference with LMWH (standard dose) (95% CI) |
|---|---|---|---|---|---|
| Wound haematoma | 184 (1 study) 7-9 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.68 (0.29 to 1.59) | 129 per 1000 | 41 fewer per 1000 (from 92 fewer to 76 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 92: Clinical evidence summary: LMWH (standard dose; standard duration) + 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 LMWH (standard dose) + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 184 (1 study) 7-9 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.86 (0.52 to 1.42) | 269 per 1000 | 38 fewer per 1000 (from 129 fewer to 113 more) |
| PE | 184 (1 study) 7-9 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 20 fewer to 20 more)[c] |
| Wound infection | 184 (1 study) 7-9 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.34 (0.04 to 3.21) | 32 per 1000 | 21 fewer per 1000 (from 31 fewer to 71 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 Zero events in both arms. Risk difference calculated in Review Manager.

**Table 93: Clinical evidence summary: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)**

| Outcomes | No of | Quality of the | Relative effect | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | evidence (GRADE) | (95% CI) | Risk with LMWH (standard duration) | Risk difference with LMWH (extended duration) (95% CI) |
|---|---|---|---|---|---|
| DVT (symptomatic and asymptomatic) | 299 (1 study) 27-29 days | LOW[a] due to imprecision | RR 0.83 (0.55 to 1.25) | 257 per 1000 | 44 fewer per 1000 (from 116 fewer to 64 more) |
| PE | 438 (1 study) 27-29 days | LOW[a] due to imprecision | Peto OR 0.14 (0.01 to 2.20) | 9 per 1000 | 8 fewer per 1000 (from 9 fewer to 11 more) |
| Major bleeding | 438 (1 study) 27-29 days | LOW[a] due to imprecision | Peto OR 0.14 (0 to 6.95) | 5 per 1000 | 4 fewer per 1000 (from 5 fewer to 26 more) |
| Heparin-induced thrombocytopaenia | 438 (1 study) 27-29 days | LOW[a] due to imprecision | RR 1.02 (0.14 to 7.17) | 9 per 1000 | 0 more per 1000 (from 8 fewer to 56 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 94: Clinical evidence summary: LMWH (standard dose; standard duration) + AES versus LMWH (low dose; standard duration) + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH (low dose) + AES | Risk difference with LMWH (standard dose) (95% CI) + AES |
| DVT (symptomatic and asymptomatic) | 152 (1 study) 14 days | LOW[a,b] due to risk of bias, imprecision | RR 0.78 (0.52 to 1.16) | 436 per 1000 | 96 fewer per 1000 (from 209 fewer to 70 more) |
| PE | 152 (1 study) 90 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.05 (0.07 to 16.55) | 13 per 1000 | 1 more per 1000 (from 12 fewer to 199 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<br>b 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) + 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 (standard dose) + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 153 (1 study) 14 days | LOW[a,b] due to risk of bias, imprecision | RR 0.56 (0.39 to 0.80) | 608 per 1000 | 267 fewer per 1000 (from 122 fewer to 371 fewer) |
| PE | 153 (1 study) 90 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.07 (0.07 to 16.76) | 13 per 1000 | 1 more per 1000 (from 12 fewer to 199 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 96: 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) |
| Major bleeding | 180 (1 study) 14 days | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 7.23 (0.14 to 364.38) | 0 per 1000 | -[a] |

a Absolute effects could not be calculated due to zero events in the control arm
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 97: Clinical evidence summary: LMWH (standard dose; standard duration) + CPM versus CPM**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with CPM | Risk difference with LMWH (standard dose) + CPM (95% CI) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with CPM | Risk difference with LMWH (standard dose) + CPM (95% CI) |
| DVT (symptomatic and asymptomatic) | 50<br>(1 study)<br>6-10 days | LOW[b]<br>due to imprecision | OR 0.14<br>(0.00 to 6.82) | 40 per 1000 | 34 fewer per 1000<br>(from 40 fewer to 181 more) |
| PE | 50<br>(1 study)<br>time-point not reported | VERY LOW[a,b,d]<br>due to risk of bias, indirectness, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 70 fewer to 70 more)[c] |
| Major bleeding | 50<br>(1 study)<br>time-point not reported | VERY LOW[a,b,d]<br>due to risk of bias, indirectness, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 70 fewer to 70 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 Zero events in both arms. Risk difference calculated in Review Manager.

d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 98: Clinical evidence summary: LMWH (low dose; standard duration) versus no pharmacological prophylaxis**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with No pharmacological prophylaxis | Risk difference with LMWH (low dose) (95% CI) |
| Major bleeding | 178<br>(1 study)<br>14 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.13<br>(0.02 to 0.94) | 45 per 1000 | 39 fewer per 1000<br>(from 3 fewer to 44 fewer) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with No pharmacological prophylaxis | Risk difference with LMWH (low 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 confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 99: Clinical evidence summary: LMWH (low 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 (low dose) + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 157 (1 study) 14 days | LOW[a,b] due to risk of bias, imprecision | RR 0.72 (0.53 to 0.98) | 608 per 1000 | 170 fewer per 1000 (from 12 fewer to 286 fewer) |
| PE | 157 (1 study) 90 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.01 (0.06 to 15.91) | 13 per 1000 | 0 more per 1000 (from 12 fewer to 189 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 100: 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 | 131 (1 study) 14 days | LOW[b] due to imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000 (from 30 fewer to 30 more)[a] |
| DVT (symptomatic and | 129 (1 study) | HIGH | RR 0.29 | 578 per 1000 | 410 fewer 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 (high dose) (95% CI) |
| asymptomatic) | 14 days | | (0.16 to 0.52) | | (from 278 fewer to 486 fewer) |
| Major bleeding | 131<br>(1 study)<br>14 days | LOW[b]<br>due to imprecision | Peto OR 0.13<br>(0 to 6.72) | 15 per 1000 | 13 fewer per 1000<br>(from 15 fewer to 80 more) |

a Zero events in both arms. Risk difference calculated in Review Manager.
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 101: 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 (high dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 288<br>(1 study)<br>15 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.72<br>(0.56 to 0.93) | 538 per 1000 | 151 fewer per 1000<br>(from 38 fewer to 237 fewer) |
| PE | 288<br>(1 study)<br>15 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.13<br>(0.00 to 6.73) | 7 per 1000 | 6 fewer per 1000<br>(from 7 fewer to 38 more) |
| Major bleeding | 453<br>(1 study)<br>15 days | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | RR 0.99<br>(0.2 to 4.84) | 13 per 1000 | 0 fewer per 1000<br>(from 11 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 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

**Table 102: Clinical evidence summary: LMWH (high dose; standard duration) 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 (high dose) (95% CI) |
| All-cause mortality | 1237<br>(3 studies)<br>15 days | LOW[a]<br>due to imprecision | Peto OR 0.37<br>(0.05 to 2.66) | 5 per 1000 | 3 fewer per 1000<br>(from 5 fewer to 8 more) |
| DVT (symptomatic and asymptomatic) | 984<br>(3 studies)<br>15 days | MODERATE[a]<br>due to imprecision | RR 0.63<br>(0.53 to 0.75) | 438 per 1000 | 162 fewer per 1000<br>(from 109 fewer to 206 fewer) |
| PE | 984<br>(3 studies)<br>15 days | LOW[a]<br>due to imprecision | Peto OR 0.76<br>(0.17 to 3.37) | 8 per 1000 | 2 fewer per 1000<br>(from 7 fewer to 19 more) |
| Major bleeding | 1319<br>(3 studies)<br>15 days | LOW[a]<br>due to imprecision | RR 1.61<br>(0.74 to 3.51) | 15 per 1000 | 9 more per 1000<br>(from 4 fewer to 38 more) |
| Fatal PE | 218<br>(1 study)<br>12±2 days | VERY LOW[a,c]<br>due to risk of bias, imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[b] |
| Wound haematoma | 670<br>(1 study)<br>14 days | LOW[a]<br>due to imprecision | RR 0.99<br>(0.06 to 15.83) | 3 per 1000 | 0 fewer per 1000<br>(from 3 fewer to 44 more) |
| Wound infection | 300<br>(1 study)<br>12±2 days | VERY LOW[a,c]<br>due to risk of bias, imprecision | RR 0.34<br>(0.04 to 3.21) | 20 per 1000 | 13 fewer per 1000<br>(from 19 fewer to 44 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 Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager

c Downgrades 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 103: Clinical evidence summary: LMWH (high dose; standard duration) versus fondaparinux**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux | Risk difference with LMWH (high dose) (95% CI) |
| Major bleeding | 1034<br>(1 study)<br>49 days | LOW[a,b]<br>due to risk of bias, indirectness | RR 0.09<br>(0.01 to 0.70) | 21 per 1000 | 19 fewer per 1000<br>(from 6 fewer to 21 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 outcome definition reported did not meet definition of outcome in protocol

**Table 104: Clinical evidence summary: LMWH (high dose; standard duration) + AES versus fondaparinux + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux + AES | Risk difference with LMWH (high dose) + AES (95% CI) |
| All-cause mortality | 1034<br>(1 study)<br>49 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 1.5<br>(0.25 to 8.94) | 4 per 1000 | 2 more per 1000<br>(from 3 fewer to 31 more) |
| DVT (symptomatic and asymptomatic) | 722<br>(1 study)<br>49 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 2.18<br>(1.58 to 3) | 125 per 1000 | 147 more per 1000<br>(from 72 more to 249 more) |
| PE | 1034<br>(1 study)<br>49 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 4<br>(0.45 to 35.67) | 2 per 1000 | 6 more per 1000<br>(from 1 fewer to 67 more) |
| Fatal PE | 1034<br>(1 study)<br>49 days | VERY LOW[a,d]<br>due to risk of bias, indirectness | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 0 fewer to 0 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 Zero events in both arms. Risk difference calculated in Review Manager.

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Fondaparinux + AES | Risk difference with LMWH (high dose) + AES (95% CI) |
| d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol | | | | | |

**Table 105: Clinical evidence summary: LMWH (high 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 (high dose) (95% CI) |
| All-cause mortality | 3485 (2 studies) 60 days | LOW[a] due to imprecision | RR 1.68 (0.48 to 5.79) | 2 per 1000 | 2 more per 1000 (from 1 fewer to 11 more) |
| DVT (symptomatic and asymptomatic) | 2581 (2 studies) 14 days | MODERATE[a] due to imprecision | RR 1.10 (0.85 to 1.41) | 81 per 1000 | 8 more per 1000 (from 12 fewer to 33 more) |
| PE | 3512 (2 studies) 14 days | LOW[a,b] due to imprecision, inconsistency | RR 0.87 (0.42 to 1.78) | 8 per 1000 | 1 fewer per 1000 (from 5 fewer to 6 more) |
| Major bleeding | 3638 (2 studies) 14 days | LOW[a,b] due to imprecision, inconsistency | RR 1.63 (0.83 to 3.19) | 8 per 1000 | 5 more per 1000 (from 1 fewer to 17 more) |
| Fatal PE | 3195 (2 studies) 14 days | LOW[a] due to imprecision | Peto OR 0.14 (0.01 to 2.17) | 1 per 1000 | 1 fewer per 1000 (from 1 fewer to 1 more) |
| Clinically relevant non-major bleeding | 3184 (1 study) 14 days | MODERATE[a] due to imprecision | RR 1.35 (0.88 to 2.08) | 22 per 1000 | 8 more per 1000 (from 3 fewer to 24 more) |
| Wound infection | 454 (1 study) | LOW[a] due to imprecision | RR 0.34 (0.04 to | 20 per 1000 | 13 fewer per 1000 (from 19 fewer to 36 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 (high dose) (95% CI) |
| | 14 days | | 2.81) | | |

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 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.

**Table 106: Clinical evidence summary: LMWH (high dose; standard duration) versus dabigatran**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Dabigatran | Risk difference with LMWH (high dose) (95% CI) |
| All-cause mortality | 1725 (1 study) 18 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.13 (0 to 6.73) | 1 per 1000 | 1 fewer per 1000 (from 1 fewer to 7 more) |
| DVT (symptomatic and asymptomatic) | 1736 (1 study) 18 days | LOW[a,b] due to risk of bias imprecision | RR 0.82 (0.68 to 0.98) | 300 per 1000 | 54 fewer per 1000 (from 6 fewer to 96 fewer) |
| PE | 1247 (1 study) 18 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.78 (0.24 to 2.55) | 10 per 1000 | 2 fewer per 1000 (from 8 fewer to 15 more) |
| Major bleeding | 1725 (1 study) 18 days | MODERATE[a] due to imprecision | RR 2.37 (0.84 to 6.7) | 6 per 1000 | 8 more per 1000 (from 1 fewer to 33 more) |
| Clinically relevant non-major bleeding | 1725 (1 study) 18 days | LOW[a] due to imprecision | RR 0.9 (0.5 to 1.62) | 27 per 1000 | 3 fewer per 1000 (from 13 fewer to 17 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 107: Clinical evidence summary: LMWH (high dose; standard duration) versus rivaroxaban**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Rivaroxaban | Risk difference with LMWH (high dose) (95% CI) |
| All-cause mortality | 3034 (1 study) 35 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.76 (0.17 to 3.39) | 3 per 1000 | 1 fewer per 1000 (from 2 fewer to 6 more) |
| DVT (symptomatic and asymptomatic) | 1924 (1 study) 17 days | LOW[a,b] due to risk of bias, imprecision | RR 1.42 (1.03 to 1.95) | 63 per 1000 | 27 more per 1000 (from 2 more to 60 more) |
| PE | 3034 (1 study) 17 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 2.02 (0.61 to 6.71) | 3 per 1000 | 3 more per 1000 (from 1 fewer to 15 more) |
| Major bleeding | 3148 (1 study) 17 days | MODERATE[b] due to imprecision | RR 0.60 (0.32 to 1.11) | 17 per 1000 | 7 fewer per 1000 (from 12 fewer to 2 more) |
| Clinically relevant non-major bleeding | 3034 (1 study) 17 days | LOW[a,b] due to risk of bias, imprecision | RR 0.78 (0.49 to 1.25) | 26 per 1000 | 6 fewer per 1000 (from 13 fewer to 6 more) |
| Wound infection | 3034 (1 study) 17 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.76 (0.17 to 3.39) | 3 per 1000 | 1 fewer per 1000 (from 2 fewer to 6 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 108: Clinical evidence summary: Fondaparinux versus no pharmacological prophylaxis**

| Outcomes | No of | Quality of the evidence | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | effect (95% CI) | Risk with No pharmacological prophylaxis | Risk difference with Fondaparinux (95% CI) |
|---|---|---|---|---|---|
| Major bleeding | 171<br>(1 study)<br>11-17 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 1.04<br>(0.07 to 16.29) | 11 per 1000 | 0 more per 1000<br>(from 11 fewer to 176 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 109: Clinical evidence summary: Fondaparinux + 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 Fondaparinux + AES (95% CI) |
| All-cause mortality | 319<br>(2 studies)<br>11-17 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[a] |
| DVT (symptomatic and asymptomatic) | 148<br>(1 study)<br>7 days | HIGH | RR 0.26<br>(0.1 to 0.67) | 257 per 1000 | 190 fewer per 1000<br>(from 85 fewer to 231 fewer) |
| PE | 148<br>(1 study)<br>7 days | LOW[b]<br>due to imprecision | Not estimable[a] | Not estimable | 0 fewer per 1000<br>(from 30 fewer to 30 more)[a] |
| Major bleeding | 171<br>(1 study)<br>11-17 days | VERY LOW[b,c]<br>due to risk of bias, imprecision | RR 1.04<br>(0.07 to 16.29) | 11 per 1000 | 0 more per 1000<br>(from 11 fewer to 176 more) |

a Zero events in both arms. Risk difference calculated in Review Manager.
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 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 110: Clinical evidence summary: Fondaparinux + IPCD + AES versus VKA + IPCD + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with VKA + IPCD + AES | Risk difference with Fondaparinux + IPCD + AES (95% CI) |
| All-cause mortality | 118 (1 study) 30 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] |
| DVT (symptomatic and asymptomatic) | 118 (1 study) 30 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] |
| PE | 118 (1 study) 30 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 111: Clinical evidence summary: Apixaban 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 Apixaban (95% CI) |
| All-cause mortality | 317 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 4.59 (0.07 to 284.39) | 0 per 1000 | -[d] |
| DVT (symptomatic and asymptomatic) | 317 (1 study) 14 days | MODERATE[a] due to risk of bias | RR 0.38 (0.23 to 0.63) | 266 per 1000 | 165 fewer per 1000 (from 98 fewer to 205 fewer) |
| PE | 317 (1 study) | VERY LOW[a,b] due to risk of bias, | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 10 fewer to 10 more)[c] |

| 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 Apixaban (95% CI) |
| | 14 days | imprecision | | | |
| Major bleeding | 456<br>(1 study)<br>14 days | LOW[b]<br>due to imprecision | Peto OR 4.50<br>(0.56 to 36.39) | 0 per 1000 | -[d] |
| Fatal PE | 317<br>(1 study)<br>7 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 4.59<br>(0.07 to 284.39) | 0 per 1000 | -[d] |
| Wound infection | 456<br>(1 study)<br>14 days | LOW[b]<br>due to imprecision | RR 0.99<br>(0.25 to 3.90) | 20 per 1000 | 0 fewer per 1000<br>(from 15 fewer to 58 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 Zero events in both arms. Risk difference calculated in Review Manager.
d Absolute effects could not be calculated due to zero events in the control arm.

**Table 112: Clinical evidence summary: Dabigatran 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 Dabigatran (95% CI) |
| All-cause mortality | 253<br>(1 study)<br>14 days | LOW[b]<br>due to imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[a] |
| DVT (symptomatic and asymptomatic) | 197<br>(1 study)<br>14 days | MODERATE[c]<br>due to risk of bias | RR 0.42<br>(0.29 to 0.63) | 564 per 1000 | 327 fewer per 1000<br>(from 209 fewer to 401 fewer) |
| PE | 253 | LOW[b] | Not | Not estimable[a] | 0 fewer 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 Dabigatran (95% CI) |
| | (1 study)<br>14 days | due to imprecision | estimable[a] | | (from 20 fewer to 20 more)[a] |
| Major bleeding | 253<br>(1 study)<br>14 days | LOW[b]<br>due to imprecision | Peto OR 2.64<br>(0.37 to 19.00) | 8 per 1000 | 13 more per 1000<br>(from 5 fewer to 126 more) |
| Clinically relevant non-major bleeding | 253<br>(1 study)<br>14 days | LOW[b]<br>due to imprecision | RR 0.64<br>(0.11 to 3.77) | 24 per 1000 | 9 fewer per 1000<br>(from 22 fewer to 67 more) |

a Zero events in both arms. Risk difference calculated in Review Manager.
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 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 113: Clinical evidence summary: Rivaroxaban 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 Rivaroxaban (95% CI) |
| DVT (symptomatic and asymptomatic) | 212<br>(1 study)<br>28 days | HIGH | RR 0.18<br>(0.05 to 0.59) | 164 per 1000 | 134 fewer per 1000<br>(from 67 fewer to 155 fewer) |
| PE | 212<br>(1 study)<br>28 days | VERY LOW[a,c,d]<br>due to risk of bias, indirectness, imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[b] |

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 Zero events in both arms. Risk difference calculated in Review Manager.
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

| 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 Rivaroxaban (95% CI) |
| d 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: Foot pump 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 Foot pump (95% CI) |
| DVT (symptomatic and asymptomatic) | 60<br>(1 study)<br>10 days | MODERATE[a]<br>due to risk of bias | RR 0.3<br>(0.13 to 0.7) | 594 per 1000 | 416 fewer per 1000<br>(from 178 fewer to 517 fewer) |
| PE | 60<br>(1 study)<br>time-point not reported | VERY LOW[a,c,d]<br>due to risk of bias, indirectness, imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000<br>(from 60 fewer to 60 more)[b] |
| 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<br>b Zero events in both arms. Risk difference calculated in Review Manager.<br>c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol<br>d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. | | | | | |

**Table 115: Clinical evidence summary: AES 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 (95% CI) |
| DVT (symptomatic and asymptomatic) | 220<br>(1 study)<br>30 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.58<br>(0.32 to 1.07) | 218 per 1000 | 92 fewer per 1000<br>(from 148 fewer to 15 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 AES (95% CI) |
| PE | 220<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 1.00<br>(0.06 to 16.09) | 9 per 1000 | 0 fewer per 1000<br>(from 9 fewer to 120 more) |
| Major bleeding | 220<br>(1 study)<br>time-point not reported | VERY LOW[a,b,d]<br>due to risk of bias, indirectness imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[c] |
| Technical complications of mechanical interventions | 220<br>(1 study)<br>time-point not reported | VERY LOW[a,b,d]<br>due to risk of bias, indirectness imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[c] |
| Wound infection | 220<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 1.00<br>(0.14 to 6.97) | 18 per 1000 | 0 fewer per 1000<br>(from 16 fewer to 96 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 Zero events in both arms. Risk difference calculated in Review Manager.

d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 116: Clinical evidence summary: IPCD 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 IPCD (95% CI) |
| DVT (symptomatic and asymptomatic) | 220<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.38<br>(0.18 to 0.77) | 218 per 1000 | 135 fewer per 1000<br>(from 50 fewer to 179 fewer) |

| 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 IPCD (95% CI) |
| PE | 220<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.14<br>(0.00 to 6.82) | 9 per 1000 | 8 fewer per 1000<br>(from 9 fewer to 50 more) |
| Major bleeding | 220<br>(1 study)<br>time-point not reported | VERY LOW[a,b,d]<br>due to risk of bias, indirectness imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[c] |
| Technical complications of mechanical interventions | 220<br>(1 study)<br>time-point not reported | VERY LOW[a,b,d]<br>due to risk of bias, indirectness imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[c] |
| Wound infection | 220<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.51<br>(0.14 to 6.97) | 18 per 1000 | 9 fewer per 1000<br>(from 17 fewer to 66 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 Zero events in both arms. Risk difference calculated in Review Manager.

d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 117: Clinical evidence summary: IPCD 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 IPCD (95% CI) |
| DVT (symptomatic and asymptomatic) | 220<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.64<br>(0.29 to 1.42) | 127 per 1000 | 46 fewer per 1000<br>(from 90 fewer to 53 more) |

| 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 (95% CI) |
| PE | 220 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.14 (0.00 to 6.82) | 9 per 1000 | 8 fewer per 1000 (from 9 fewer to 50 more) |
| Major bleeding | 220 (1 study) time-point not reported | VERY LOW[a,b,d] due to risk of bias, indirectness imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 20 fewer to 20 more)[c] |
| Technical complications of mechanical interventions | 220 (1 study) time-point not reported | VERY LOW[a,b,d] due to risk of bias, indirectness imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 20 fewer to 20 more)[c] |
| Wound infection | 220 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.51 (0.05 to 4.96) | 18 per 1000 | 9 fewer per 1000 (from 17 fewer to 66 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 Zero events in both arms. Risk difference calculated in Review Manager.
d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 118: Clinical evidence summary: CPM 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 CPM (95% CI) |
| DVT (symptomatic and asymptomatic) | 65 (1 study) 90 days | VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000 (from 60 fewer to 60 more)[a] |

| 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 CPM (95% CI) |

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 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.

## 27.4 Economic evidence

**Published literature**

Thirty economic studies, in 32 publications, relating to this review question were identified but were excluded due limited applicability, methodological limitations, a combination of limited applicability and methodological limitations or the availability of more applicable evidence.[10,32,33,39,47,75,79,80,117,119,126,128,197,207,208,214,224,226,228-230,246,253-255,259,281,282,305,320,321,329] Of these, 10 publications were previously included in CG46.[10,32,33,68,70,79,119,126,197,253] They also included 3 NICE TAs, 2 evidence review group [ERG] reports and the CG92 model for standard duration and post discharge prophylaxis. All excluded studies are listed in appendix O, with reasons for exclusion given.

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

**New cost-effectiveness analysis**

The committee considered the available evidence of cost effectiveness of prophylaxis strategies for people admitted for elective knee replacement (eTKR). The original guideline (CG92) model was considered but it was considered that it required updating given the availability of more recent trial data and the exclusion of the some of the older studies that were included in the CG92 NMAs from the current updated NMAs. The original model also included some interventions that are not routinely used in current practice including high doses of aspirin, VKA and UFH. The committee also discussed that since the publication of CG92, three TAs covering the use of DOACs in this population have also been published the latest in 2012.[228-230] It was agreed that it would be more convenient for clinicians to be able to consult a single source for recommendation regarding the most cost- effective prophylaxis strategy for this population. This would also help in standardising current practice. Moreover, as the size of the population covered by this review question is very large; which means that changes to more costly prophylaxis options would lead to substantial resource implications, the committee agreed that this question should be prioritised for economic modelling. Hence, the original economic model presented here sought to address the question about the cost-effectiveness of different VTE prophylaxis strategies (alone or in combination) in people admitted for eTKR. A summary of the analysis is presented below and a full description can be found in appendix P in the full guideline.

**Model overview**

A cost-utility analysis was undertaken in Microsoft Excel® where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services (PSS) perspective. A Markov model was constructed in order to estimate the costs and QALYs associated with different VTE prophylaxis strategies. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance[231] Uncertainty was explored through probabilistic and sensitivity analyses. The time horizon considered was lifetime.

**Population**

The population entering the model are adults who are admitted to hospital for an eTKR. The cohort characteristics were based on the data reported in the National Joint Registry 13th annual report;[36] which represented data collected up to December 2015 in England, Wales, Northern Ireland and the Isle of Man. The mean age of this population was 69.3 years and 44% were male.

**Comparators**

Thirteen prophylaxis strategies were selected for inclusion based on the availability of evidence from the clinical review, direct and network meta-analyses (N)MAs and discussion with the committee around which regimens are considered to be relevant to current clinical practice in the UK. These were:

1. LMWH (std,std) + AEs
2. Fondaparinux+ AES
3. Foot pump + AES
4. IPCD
5. Foot pump
6. AES
7. LMWH (std,std)
8. LMWH (std,extd)
9. Aspirin
10. Dabigatran
11. Apixaban
12. Rivaroxaban
13. No prophylaxis

**Model structure**

The model consists of a simple decision tree covering the acute phase from admission up to 90 days post-operatively, to cover the period included in the definition of hospital-acquired VTE, followed by a Markov chain for the remaining model time horizon. The structure is repeated for each prophylaxis strategy.

The acute phase of the model is represented by a decision tree consisting of the primary clinical events: DVT (symptomatic proximal, symptomatic distal, asymptomatic proximal and asymptomatic distal), non-fata PE, fatal PE, Surgical site bleeding, non-surgical site bleeding (gastrointestinal (GI) bleeding, intracranial haemorrhage (ICH)/haemorrhagic stroke, other major bleeding), fatal major bleeding (MB), clinically-relevant non-major bleeding (CRNMB) and heparin-induced thrombocytopaenia (HIT).The structure of the decision tree is presented in Figure 4.

The long-term part is represented by a Markov cohort model. Individuals enter the model in one of the following states; based on where they end up at the end of the 90 days post-operatively: Well, post-symptomatic proximal DVT, post-symptomatic distal DVT, post-asymptomatic proximal DVT, post-asymptomatic distal DVT, post-PE, amputated post-HIT, disabled post-stroke, post-revision for infection. In the first two years, individuals in a post-VTE state can develop post-thrombotic syndrome (PTS). Those in the post-PE state can also develop chronic thromboembolic pulmonary hypertension (CTEPH). Transitioning to death is allowed from any state in the model, to represent all-cause mortality. The structure of the Markov cohort model is illustrated in Figure 5.

**Model inputs**

The relative effects of treatments on the baseline transition probabilities were derived from clinical evidence identified in the systematic review undertaken for the guideline, the results of the NMA and supplemented by additional data sources as required. Health utility data were obtained from the literature. Cost inputs were obtained from recognized national sources such as the drug tariff, NHS reference costs and Personal Social Services Research Unit (PSSRU) publications. All inputs and assumptions made were validated by the committee.

**Sensitivity analysis**

A probabilistic analysis was carried out whereby distributions were assigned to model inputs in order to account for the uncertainty around the point estimates of these inputs and capture the effect of this uncertainty on model outputs. Additionally, a number of one-way sensitivity analyses were conducted whereby, for each analysis one key model input was changed in order to explore the sensitivity of model results to changes in that parameter (Table 119).

**Table 119: One-way sensitivity analyses**

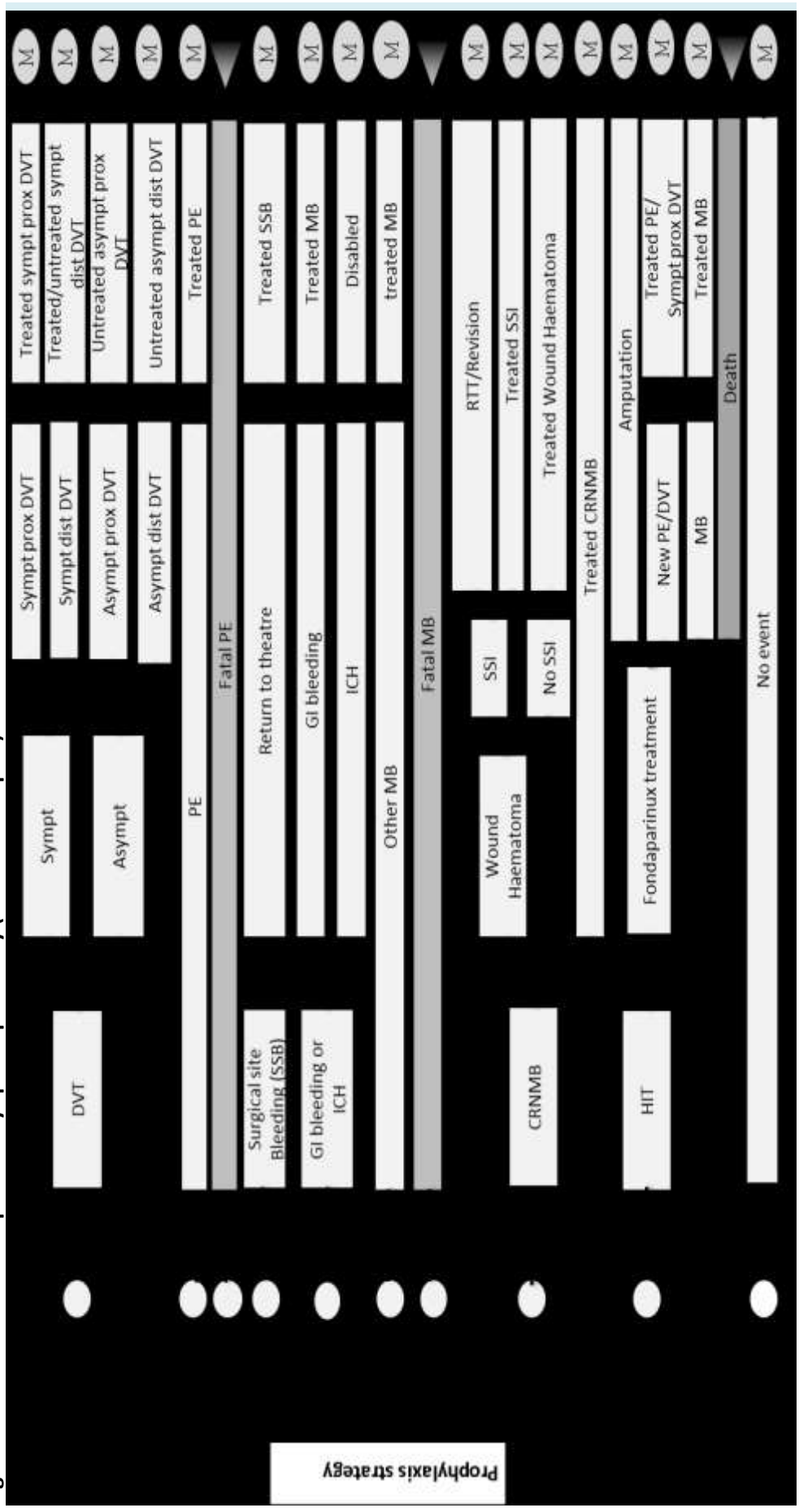
| | description | Base case input value | Alternative value for sensitivity analysis |
|---|---|---|---|
| SA1 | Cost effectiveness threshold | £20,000 | £30,000 |
| SA2 | Discount rate for costs and QALYs | 3.5% | 1.5% |
| SA3 | Prophylaxis duration | Based on the RCTs included in the DVT NMA | based on summary of product characteristics (SmPC) |
| SA4 | Cohort starting age | eTKR: 69.3 years (a) | 40 years |
| SA5 | Cohort body weight | NJR cohort mean body weight(a) | Cohort body weight distribution calculated based on the NJR cohort BMI distribution (a) and average height for a UK male (1.75m) and female (1.62 m) (b) |
| SA6 | All costs +10% | See appendix P | Costs increased by 10% |
| SA7 | All costs -10% | See appendix P | Costs decreased by 10% |
| SA8 | Timing of VTE and MB events | Based on committee expert opinion | Based on data from Warwick 2007[308] |
| SA9 | Risk of VTE recurrence after :<br><br>Treated DVT<br>PE | Assumption based on committee opinion<br><br>0%<br>0% | Calculated based on data from TA245 manufacturer submissions<br><br>2.74%<br>0.26% |
| SA10 | Costs of pharmacological prophylaxis | Calculated assuming no wastage | Calculated taking possible wastage into account |

*Abbreviations: eTKR: elective total knee replacement; NMA: network meta-analysis; SA: sensitivity analysis*

*(a) Source: National Joint Registry[36]*

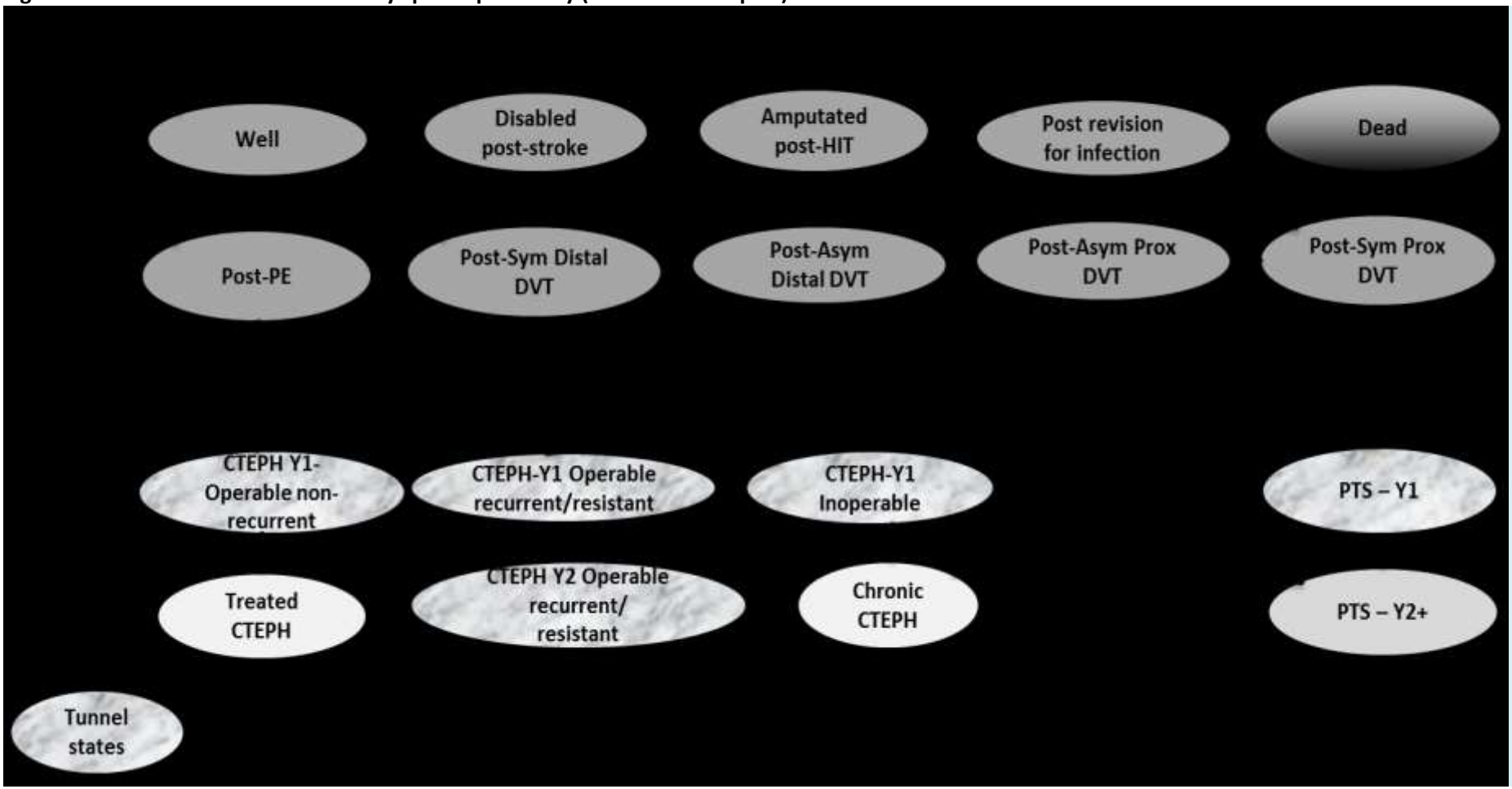
*(b) Source: ONS [237]*

**Figure 4: Model structure up to 90 days post-operatively (Decision tree part)**




*Abbreviations: Asympt: asymptomatic; Dist: distal; DVT: Deep vein thrombosis; GI: gastrointestinal; HIT: heparin-induced thrombocytopaenia; ICH: intracranial haemorrhage; MB: major bleeding; PE: pulmonary embolism; Prox: proximal; RTT: return to theatre; SSB: surgical site bleeding, SSI: surgical site infection; Sympt: symptomatic*

**Figure 5: Model structure after 90 days post-operatively (Markov model part)**




*Abbreviations: Asympt: asymptomatic; CTEPH: chronic thrombo-embolic pulmonary hypertension; DVT: Deep vein thrombosis; HIT: heparin-induced thrombocytopaenia; PE: pulmonary embolism; Prox: proximal; PTS: post-thrombotic syndrome; Sympt: symptomatic*

**Results**

***Base case***

The results of the base case analysis are presented in Table 120 and Figure 6. These show that the most effective intervention in terms of QALYs- gained is foot pump, with mean discounted QALYs per patient of 9.814 (95% CI: 7.86 to 11.58) over life-time time horizon followed by aspirin, with mean discounted QALYs per patient of 9.809 (95% CI: 7.86 to 11.58) and LMWH (standard dose, standard duration)+AES with a mean of 9.807 (95% CI: 7.86 to 11.58) over life-time time horizon. The least effective was dabigatran; with 9.71 QALYs (95% CI: 7.53 to 11.56). Aspirin had the lowest mean total cost of £187 (95% CI: £118 to £304) followed by foot pump with a mean total cost of £219 (95% CI: £119 to £473) and rivaroxaban with a mean total cost of £256 (95% CI: £82 to £1,205). The highest mean total cost was seen for fondaparinux + AES; with mean total cost of £904 (95% CI: £358 to £3,016).

The incremental net monetary benefit (INMB) vs the comparator (LMWH [standard, dose, standard duration]+ AES) was calculated at a cost-effectiveness threshold of £20,000 per QALY gained. Based on the INMB, the most cost-effective strategy (the one with the highest INMB) was found to be foot pump; with mean INMB of £353 (95% CI: -£101 to £665); with 18% probability of being the most cost-effective. It was followed by aspirin, with mean INMB of £281
(95% CI: -£195 to £703), then foot pump + AES (mean INMB £72 [95% CI: -£379 to £343]).

The full ranking based on the mean INMB of each strategy; together with the 95% confidence intervals that were calculated probabilistically, are presented in Table 120. This shows that there is considerable uncertainty in relation to the ranking of these interventions; with wide and overlapping 95% CIs. Based on the rank of the INMB; all interventions except dabigatran were more cost-effective than no prophylaxis. Foot pump and IPCD were more cost-effective compared to AES in this population.

Of the DOACs included in the model; rivaroxaban dominated both apixaban and dabigatran. However, the model comparator (LMWH [standard dose, standard duration]+AES) was more cost-effective compared to rivaroxaban (ICER: £7,686).

***Sensitivity analysis***

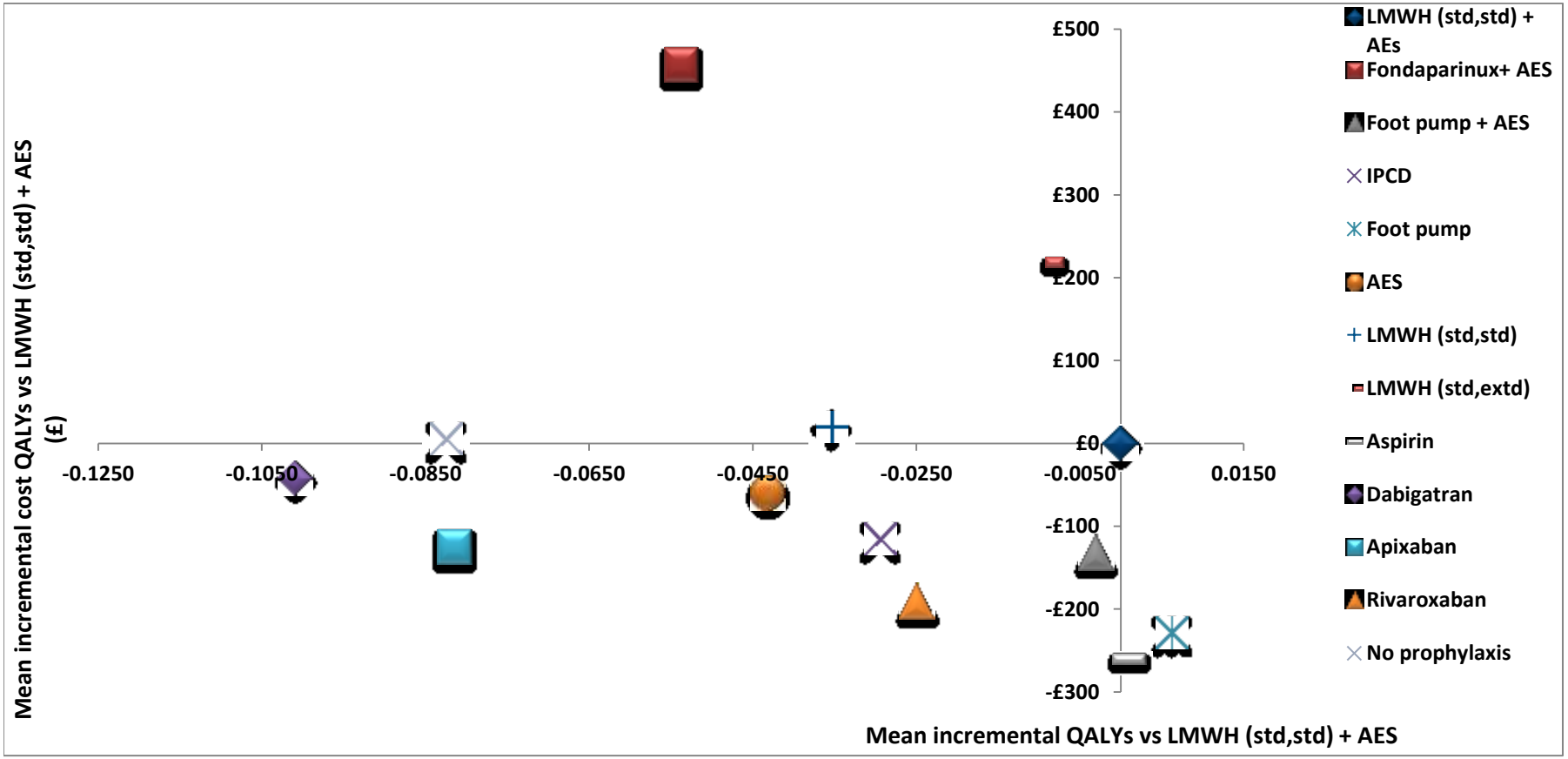
In all the SAs undertaken, the most cost effective option (foot pump) and the ranking of all interventions remained largely the same.

**Table 120: Probabilistic base case analysis results for elective total knee replacement (eTKR) population**

| Intervention | Mean discounted QALYs (95% CI) | Mean Discounted Costs (95% CI) | Incremental QALYs vs LMWH+ AEs (95% CI) | Incremental costs vs LMWH+ AEs (95% CI) | Mean INMB at £20K (95% CI) | Probability most CE option (95% CI) | Rank (95% CI) |
|---|---|---|---|---|---|---|---|
| **LMWH (std,std) + AEs** | **9.81** (7.86 to 11.58) | **£448** (£364 to £613) | **0.000** (0.000 to 0.000) | **£0** (£0 to £0) | **£0** (£0 to £0) | 0.1% | **4** (4, 12) |
| **Fondaparinux+ AES** | **9.75** (7.83 to 11.52) | **£904** (£358 to £3016) | **-0.054** (-0.183 to -0.009) | **£457** (-£53 to £2466) | **-£1,532** (-£6,183 to -£176) | 0.0% | **11** (6, 13) |
| **Foot pump + AES** | **9.80** (7.86 to 11.58) | **£315** (£208 to £590) | **-0.003** (-0.020 to 0.006) | **-£132** (-£234 to £32) | **£72** (-£379 to £343) | 0.1% | **3** (3, 12) |
| **IPCD** | **9.78** (7.82 to 11.56) | **£332** (£133 to £1246) | **-0.029** (-0.367 to 0.019) | **-£115** (-£304 to £698) | **-£473** (-£8,223 to £635) | 5.8% | **7** (1, 13) |
| **Foot pump** | **9.81** (7.86 to 11.58) | **£219** (£119 to £473) | **0.006** (-0.011 to 0.018) | **-£228** (-£332 to -£65) | **£353** (-£101 to £665) | 18.1% | **1** (1, 10) |
| **AES** | **9.76** (7.77 to 11.57) | **£387** (£167 to £1397) | **-0.043** (-0.420 to 0.014) | **-£60** (-£271 to £876) | **-£803** (-£9,251 to £520) | 0.2% | **9** (3, 13) |
| **LMWH (std,std)** | **9.77** (7.79 to 11.55) | **£468** (£287 to £1563) | **-0.035** (-0.441 to 0.018) | **£21** (-£105 to £989) | **-£728** (-£10,057 to £445) | 0.0% | **8** (4, 11) |
| **LMWH (std,extd)** | **9.80** (7.85 to 11.58) | **£666** (£508 to £1302) | **-0.009** (-0.111 to 0.023) | **£218** (£34 to £832) | **-£398** (-£3,013 to £397) | 0.1% | **6** (3, 12) |
| **Aspirin** | **9.81** (7.86 to 11.58) | **£187** (£118 to £304) | **0.001** (-0.018 to 0.014) | **-£260** (-£436 to -£125) | **£281** (-£195 to £703) | 9.0% | **2** (1, 12) |
| **Dabigatran** | **9.71** (7.53 to 11.56) | **£406** (£100 to £2987) | **-0.101** (-1.308 to 0.020) | **-£42** (-£343 to £2524) | **-£1,977** (-£28,720 to £707) | 3.6% | **13** (1, 13) |
| **Apixaban** | **9.73** (7.62 to 11.54) | **£322** (£69 to £2624) | **-0.081** (-1.178 to 0.023) | **-£125** (-£392 to £2166) | **-£1,504** (-£25,838 to £802) | 42.8% | **10** (1, 13) |
| **Rivaroxaban** | **9.78** (7.79 to 11.57) | **£256** (£82 to £1205) | **-0.025** (-0.333 to 0.021) | **-£191** (-£360 to £634) | **-£306** (-£6,975 to £747) | 19.7% | **5** (1, 11) |
| **No prophylaxis** | **9.73** (7.68 to 11.53) | **£453** (£137 to £2281) | **-0.082** (-0.894 to 0.014) | **£6** (-£298 to £1,715) | **-£1,655** (-£20,058 to £540) | 0.4% | **12** (3, 13) |

*Abbreviations: AEs: anti-embolism stockings; CE: cost effective; CI: confidence interval; eTKR: elective total knee replacement; extd: extended; IPCD: intermittent pneumatic compression devices; INMB: incremental net monetary benefit; LMWH: low molecular weight heparin; QALYs: quality-adjusted life-years; std: standard*

**Figure 6: Incremental analysis (vs LMWH (std,std)+ AES) results presented on the cost effectiveness plane**




*Abbreviations: AES: anti-embolism stockings; CE: cost-effective; CI: confidence interval; eTKR: elective total knee replacement; extd: extended; INMB: incremental net monetary benefit; IPCD: intermittent pneumatic compression device; LMWH: low molecular weight heparin; std: standard; QALYs: quality-adjusted life-years.*

**Discussion**

**Interpretation and limitations**

The results of this analysis reflect the very large uncertainty seen in the eTKR NMAs and in particular the uncertainty in the PE NMA which appeared to be driving the results of the economic model. This has been reflected in the very small differences in QALYs gained, the very wide 95% CIs around the ranks and the fact that the optimal intervention (foot pump) only had 18% probability of being the most cost-effective option. On average, however, the results seem to support the conclusion that VTE prophylaxis is cost-effective compared to no prophylaxis. However, the choice of a prophylaxis strategy is not clear cut. This is likely to be the result of the uncertainty around the relative effectiveness estimates for the different strategies.

Nevertheless, based on the results of this economic model; low intensity and lower cost strategies appeared to be more cost-effective for individuals undergoing eTKR, which might be the result of the lower risk of symptomatic DVT and PE in this population compared to the eTHR population. This has been reflected in the most cost-effective options being foot pump, aspirin and a combination of foot pump and AEs. Of the DOACs included in the model; rivaroxaban dominated both apixaban and dabigatran. This was in line with the results of the economic models assessed as part of TA170 and TA245 and a more recent analysis funded by the NIHR.[229,230,281] Of the mechanical prophylaxis options considered in the analysis, foot pumps and IPCD were more cost-effective compared to AES. This supported the clinical experience that AES are not a practical option in this population.

Similar to the eTHR population, the model was an update of the CG92 model; so we attempted to address the limitations of that model which were highlighted by the orthopaedic surgeons' community in a number of publications. One limitation was the use of relative effectiveness from the DVT NMA for the PE outcomes; where we used the PE NMA for all the interventions for which PE data were available to avoid making this assumption unless absolutely necessary; where the strategy was not included in the PE network. However, we have verified this assumption with the committee and externally validated it using the observational data analysis that used NJR data;[152] where the ratio of the relative effectiveness of LMWH vs aspirin for the DVT outcome was found to be approximately the same as for the PE outcome.

Another issue was the lack of differentiation between proximal and distal DVT. We have addressed this issue by differentiating between the proximal and distal DVT for both symptomatic and asymptomatic events. We also allowed for different probabilities of progressing from each of these DVT events to PTS; to acknowledge the fact that progression from treated and untreated DVT to PTS would be different. We emphasised the fact that asymptomatic DVT also does not have an impact on costs and outcomes in the short term as it is not diagnosed in practice and its only consequence in the model is its future progression to PTS.

There was also a concern regarding the baseline risk used in the model which was based on data from the "no prophylaxis" arm in the RCTs. This was not considered to be reflective of current incidence of VTE with some trials dating back to the 70s, especially as practice has changed in terms of encouraging early mobilisation as well as the difference in surgical techniques. Based on this, we have used a strategy consisting of LMWH (standard dose, standard duration)+AES as our model comparator and obtained its baseline risk data from observational cohort studies that used the UK NJR data (see model write-up appendix P).[152]

However, this updated model may have some limitations. Due to lack of data on either DVT or PE outcomes for some strategies, an assumption still had to be made about the equivalence of relative effectiveness on the DVT and PE outcomes for these strategies. However, we have limited this only to instances where data was available for one of these outcomes but not for the other. This

assumption may have affected the results. The relative effectiveness of foot pump, aspirin and foot pump + AES in relation to the PE outcome was assumed to be the same as their relative effectiveness obtained from the DVT NMA. This has resulted in a much lower PE rate for these interventions compared to all the others.

Another limitation of this analysis is that the relative safety of aspirin compared to LMWH was based on an observational cohort analysis based on NJR data. [152] This was due to the lack of any randomised controlled trials that report major bleeding outcomes for aspirin in these populations. However, as the data for MB from trials are likely to be imprecisely estimated due to the rarity of these events, it was considered that the use of observational data would be appropriate.

**Generalisability to other populations/settings**

This analysis has been undertaken from a UK NHS and PSS perspective; hence its results might not be generalisable beyond these settings. The population modelled also represents a cohort whose characteristics might be different from eTKR cohorts in other settings.

**Conclusions**

In people undergoing elective total knee replacement (eTKR), VTE prophylaxis appears to be cost-effective compared to no prophylaxis. Foot pump was found to be the most cost-effective option in this population. This result was robust to changes in the model input parameters. LMWH-based strategies that use standard duration are more cost-effective compared to extended duration LMWH. Rivaroxaban was found to be the most cost-effective of the DOACs considered in this analysis. These results, however, are subject to high uncertainty given the imprecise effectiveness results from the NMAs that underpinned this analysis.

## 27.5 Evidence statements

**Clinical**

**Pairwise meta-analysis statements**

**Pharmacological interventions versus pharmacological interventions**

*LMWH (standard dose; standard duration)*

LMWH at a standard dose for a standard duration was compared with no prophylaxis, the outcomes DVT (symptomatic and asymptomatic), PE, major bleeding, wound haematoma, technical complications of mechanical interventions (examples given were skin rash, swelling above the appliance, pressure necrosis of the skin and peroneal nerve palsy) and wound infection were reported in one study. Moderate quality evidence showed clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic).Very low quality evidence suggested possible clinical benefit of LMWH in terms of PE and wound infection; however the uncertainty around this result was also consistent with both no difference or clinical harm. There was possible clinical harm of LMWH in terms of wound haematoma and no clinical difference in terms of major bleeding and technical complications of mechanical interventions, however there was also considerable uncertainty around these results. The quality of the evidence ranged from very low to moderate due to risk of bias, imprecision, indirectness and inconsistency.

LMWH at a standard dose for a standard duration was compared with apixaban, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE, clinically relevant non-major bleeding and wound haematoma were reported in one study. There was possible clinical benefit of LMWH in terms of all-cause mortality, PE, fatal PE and wound haematoma. However the uncertainty around these results also related to no difference and clinical harm. Moderate quality evidence showed clinical harm of LMWH in terms of DVT (symptomatic and asymptomatic). There was possible clinical harm of LMWH in terms of major bleeding and clinically relevant non-major bleeding, although these outcomes also had serious uncertainty. The quality of the evidence ranged from very low to moderate due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration was compared with dabigatran, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE and clinically relevant non-major bleeding were reported across two studies. High quality, precise evidence showed no clinical difference between LMWH and dabigatran for DVT. There was a suggestion of clinical harm of LMWH in terms of fatal PE and no clinical difference in terms of all-cause mortality, PE, major bleeding and clinically relevant non-major bleeding, although all of these results were associated with considerable uncertainty. The quality of the evidence ranged from low to high due to imprecision. The outcome with evidence of high quality of was DVT (symptomatic and asymptomatic).

LMWH at a standard dose for a standard duration was compared with rivaroxaban, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, clinically relevant non-major bleeding and wound infection were reported across two studies. There was clinical harm of LMWH in terms of DVT (symptomatic and asymptomatic). There was, possible clinical harm of LMWH in terms of all-cause mortality, PE and wound infection, although these findings could also have been consistent with no difference. There was no clinical difference in terms of major bleeding and clinically relevant non-major bleeding, however the uncertainty around the bleeding results were also consistent with both benefit and harm. The quality of the evidence ranged from very low to moderate due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration was compared with aspirin, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was no clinical difference between the two interventions for both of the outcomes reported, although there was very serious imprecision around both results. The quality of the evidence was very low due to risk of bias, imprecision and indirectness.

LMWH at a standard dose for a standard duration was compared with UFH, the outcome wound haematoma was reported in one study. There was possible clinical benefit of LMWH in terms of this outcome of wound haematoma, however the uncertainty around this result was also consistent with no difference and clinical harm. The quality of the evidence was very low due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration was compared with LMWH at a low dose for a standard duration, the outcome major bleeding was reported in one study. There was possible clinical harm of LMWH at a standard dose in regards to this outcome, however there was very serious uncertainty around the result. The quality of the evidence of the evidence was very low due to risk of bias and imprecision.

*LMWH (standard dose; extended duration)*

LMWH at a standard dose for an extended duration was compared with LMWH at a standard dose for a standard duration, the outcomes DVT (symptomatic and asymptomatic), PE, major bleeding and heparin-induced thrombocytopaenia were reported in one study. There was possible clinical benefit of LMWH for an extended duration in terms of PE and major bleeding. There was no clinical difference in terms of DVT (symptomatic and asymptomatic) and heparin-induced thrombocytopaenia. However for all four outcomes the results were considerably uncertain and could be associated with harm, no difference and benefit. The quality of the evidence was low due to imprecision.

*LMWH (low dose; standard duration)*

LMWH at a low dose for a standard duration was compared with no prophylaxis, the outcome was major bleeding was reported in one study. There was possible clinical harm of LMWH in terms of major bleeding, however this result was uncertain and could also be consistent with no difference. The quality of evidence was very low due to risk of bias and imprecision.

*LMWH (high dose; standard duration)*

LMWH at a high dose for a standard duration was compared with no prophylaxis, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic) and major bleeding were reported in one study. High quality evidence showed clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic). Low quality evidence suggested possible clinical benefit of LMWH in terms of major bleeding and no clinical difference in terms of all-cause mortality, however there was uncertainty around both of these results. The quality of evidence ranged from low to high due to imprecision.

LMWH at a high dose for a standard duration was compared with UFH, the outcomes DVT (symptomatic and asymptomatic), PE and major bleeding were reported in one study. There was possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic) and PE. There was no clinical difference in terms of major bleeding. However all three of these outcomes were associated with a high level of uncertainty. 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 VKA, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE, wound haematoma and wound infection were reported across three studies. There was possible clinical benefit of LMWH in terms of all-cause mortality, DVT (symptomatic and asymptomatic), major bleeding and wound infection, although these results were uncertain. There was no clinical difference in terms of PE, fatal PE and wound haematoma, however these results were also uncertain. The quality of evidence ranged from very low to moderate due to risk of bias and imprecision.

LMWH at a high dose for a standard duration was compared with fondaparinux, the outcome major bleeding was reported in one study. Low quality, precise evidence showed clinical benefit of LMWH in terms of this outcome. The quality of the evidence was low due to risk of bias and indirectness.

LMWH at a high dose for a standard duration was compared with apixaban, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE, clinically relevant non-major bleeding and wound infection were reported across two studies. There was possible clinical benefit of LMWH in terms of fatal PE and wound infection. There was possible clinical harm of LMWH in terms of all-cause mortality, major bleeding and clinically relevant non-major bleeding. There was no clinical difference in terms of DVT (symptomatic and asymptomatic) and PE. There was considerable uncertainty around all of the outcomes for this comparison. The quality of the evidence ranged from low to moderate due to imprecision and inconsistency.

LMWH at a high dose for a standard duration was compared with dabigatran, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and clinically relevant non-major bleeding were reported in one study. There was possible clinical benefit of LMWH in terms of all-cause mortality, possible clinical harm in terms of major bleeding and no clinical difference in terms of major bleeding and PE. There was considerable uncertainty around all of the outcomes for this comparison. The quality of evidence ranged from very low to moderate due to risk of bias and imprecision.

LMWH at a high dose for a standard duration was compared with rivaroxaban, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, clinically relevant non-major bleeding and wound infection were reported in one study. There was possible clinical benefit of LMWH in terms of all-cause mortality and major bleeding. There was possible clinical harm of LMWH in terms of DVT (symptomatic and asymptomatic) and PE. There was no clinical difference in terms of clinically relevant non-major bleeding and wound infection. There was considerable uncertainty around all of the outcomes for this comparison. The quality of evidence ranged from very low to moderate due to risk of bias and imprecision.

*Fondaparinux*

Fondaparinux was compared with no prophylaxis, the outcome major bleeding was reported in one study. There was no clinical difference for this outcome; however the quality of the evidence was very low due to risk of bias and very serious imprecision around the effect estimate, meaning the result could also be consistent with clinical benefit or harm.

*Apixaban*

Apixaban was compared with VKA, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE and wound infection were reported one study. Moderate quality evidence showed clinical benefit of apixaban in terms of DVT (symptomatic and asymptomatic). There was possible clinical harm of apixaban in terms of all-cause mortality, major bleeding and fatal PE, however these results may also be consistent with no difference and clinical benefit as they were so uncertain. There was no clinical difference in terms of PE and wound

infection. These results were similarly uncertain. The quality of the evidence ranged from very low to moderate due to risk of bias and imprecision.

*Dabigatran*

Dabigatran was compared with no prophylaxis, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and clinically relevant non-major bleeding were reported in one study. Moderate quality, precise evidence showed clinical benefit of dabigatran in terms of DVT (symptomatic and asymptomatic). Low quality evidence suggested possible clinical benefit of dabigatran in terms of clinically relevant non-major bleeding, possible clinical harm of dabigatran in terms of major bleeding, and no clinical difference in terms of all-cause mortality and PE. There was considerable uncertainty around these results. The quality of evidence ranged from low to moderate due to risk of bias and imprecision.

*Rivaroxaban*

Rivaroxaban was compared with aspirin, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. High quality evidence showed clinical benefit of rivaroxaban in terms of DVT (symptomatic and asymptomatic). Very low quality evidence suggested no clinical difference in terms of PE, however this was uncertain. The quality of the evidence ranged from very low to high due to risk of bias, indirectness and imprecision. The outcome with evidence of high quality was DVT (symptomatic and asymptomatic).

**Pharmacological interventions versus mechanical interventions**

LMWH at a standard dose for a standard duration was compared with AES, the outcomes DVT (symptomatic and asymptomatic), PE, technical complications of mechanical interventions (examples given were skin rash, swelling above the appliance, pressure necrosis of the skin and peroneal nerve palsy) and wound infection in one study. There was possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic), PE and wound infection. There was no clinical difference in terms of technical complications of the mechanical intervention. The evidence for all four of these outcomes exhibited considerable uncertainty. 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 a standard duration was compared with IPCD, the outcomes DVT (symptomatic and asymptomatic), PE, technical complications of mechanical interventions (examples given were skin rash, swelling above the appliance, pressure necrosis of the skin and peroneal nerve palsy) and wound infection in one study. There was possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic) and wound infection. There was no clinical difference in terms of PE and technical complications of the mechanical intervention. The evidence for all four of these outcomes exhibited considerable uncertainty. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

**Combination interventions versus single interventions**

LMWH at a standard dose for a standard duration was compared with foot pump in combination with AES, the outcomes DVT (symptomatic and asymptomatic) and fatal PE were reported in one study. There was possible clinical benefit of LMWH for both outcomes, however the DVT outcome was also consistent with no difference, and the fatal PE outcome with both no difference and clinical

harm. 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 a standard duration in combination with AES was compared with AES, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was possible clinical benefit of LMWH in combination with AES in terms of DVT (symptomatic and asymptomatic) and no clinical difference in terms of PE, however there was uncertainty associated with both of these results. 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 CPM was compared with CPM, the outcomes DVT (symptomatic and asymptomatic), PE and major bleeding were reported in one study. There was possible clinical benefit in terms of DVT (symptomatic and asymptomatic). There was no clinical difference in terms of PE and major bleeding. All three outcomes has considerable uncertainty associated with them. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

LMWH at a low dose for a standard duration in combination with AES was compared with AES, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was possible clinical benefit of LMWH in combination with AES in terms of DVT (symptomatic and asymptomatic), although this finding was also consistent with no difference. And no clinical difference was suggested in terms of PE, although this finding was very uncertain and could also be consistent with benefit and harm. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

Fondaparinux in combination with AES was compared with AES, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and major bleeding were reported in one study. High quality evidence showed clinical benefit of fondaparinux in combination with AES in terms of DVT (symptomatic and asymptomatic). There was no clinical difference in terms of all-cause mortality, PE and major bleeding. However the findings for these three outcomes were also consistent with benefit and harm. The quality of the evidence ranged from very low to high due to risk of bias and imprecision. The outcome with evidence of high quality was DVT (symptomatic and asymptomatic).

**Combination interventions versus combination interventions**

*LMWH (standard dose; standard duration) + AES*

LMWH at a standard dose for a standard duration in combination with AES was compared with UFH in combination with AES, the outcomes DVT (symptomatic and asymptomatic), PE and wound infection were reported in one study. There was possible clinical benefit of LMWH in combination with AES in terms of wound infection and no clinical difference in terms of DVT (symptomatic and asymptomatic) and PE. However all three of these outcomes were associated with considerable uncertainty. The quality of the evidence was very low due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration in combination with AES was compared with foot pump in combination with AES, the outcomes DVT (symptomatic and asymptomatic) and fatal PE were reported in one study. There was possible clinical benefit of LMWH in combination with AES in terms of fatal PE, although this finding was very uncertain. There was no clinical difference suggested for DVT (symptomatic and asymptomatic), however the uncertainty around this result was also consistent with clinical benefit. The quality of evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

LMWH at a standard dose for a standard duration in combination with AES was compared with LMWH at a low dose for a standard duration in combination with AES, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. There was no clinical

difference for both of these outcomes, although there was considerable uncertainty associated with both. The quality of evidence ranged from very low to low due to risk of bias and imprecision.

*LMWH (high dose; standard duration) + AES*

LMWH at a standard dose for a standard duration in combination with AES was compared with fondaparinux in combination with AES, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and fatal PE were reported in one study. There was possible clinical harm of LMWH in combination with AES in terms of all-cause mortality, DVT (symptomatic and asymptomatic) and PE. However there was uncertainty around these results. There was no clinical difference in terms of fatal PE. The quality of the evidence ranged from very low to low due to risk of bias and imprecision and indirectness.

*Fondaparinux + IPCD + AES*

Fondaparinux in combination with IPCD and AES was compared with VKA in combination with IPCD and AES, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic) and PE were reported in one study. There was no clinical difference for all the outcomes; although all outcomes were very uncertain. The quality of the evidence was very low due to risk of bias and imprecision.

**Mechanical interventions versus mechanical interventions**

*Foot pump*

Foot pump was compared with no prophylaxis, the outcomes DVT (symptomatic and asymptomatic) and PE were reported in one study. Moderate quality evidence showed clinical benefit of foot pump in terms of DVT (symptomatic and asymptomatic) and very low quality evidence suggested no clinical difference in terms of PE. There was uncertainty around the PE result. The quality of the evidence ranged from very low to moderate due to risk of bias, indirectness and imprecision.

*AES*

AES was compared with no prophylaxis, the outcomes DVT (symptomatic and asymptomatic), PE, major bleeding, technical complications of mechanical interventions and wound infections were reported in one study. There was possible clinical benefit of AES in terms of DVT (symptomatic and asymptomatic). There was no clinical difference in terms of PE, major bleeding, technical complications of mechanical interventions and wound infection. There was considerable uncertainty around the effect estimates for all five outcomes. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

*IPCD*

IPCD was compared with no prophylaxis, the outcomes DVT (symptomatic and asymptomatic), PE, major bleeding, technical complications of mechanical interventions and wound infections were reported in one study. There was possible clinical benefit of IPCD in terms of DVT (symptomatic and asymptomatic), PE and wound infection, and no clinical difference in terms major bleeding and technical complications of mechanical interventions. However these results were all very uncertain.

The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

IPCD was compared with AES, the outcomes DVT (symptomatic and asymptomatic), PE, major bleeding, technical complications of mechanical interventions and wound infections were reported in one study. There was possible clinical benefit of AES in terms of DVT (symptomatic and asymptomatic), PE and wound infection, and no clinical difference in terms major bleeding and technical complications of mechanical interventions. However there was considerable uncertainty around all these results. The quality of the evidence was very low due to risk of bias, indirectness and imprecision.

*Continuous passive motion*

Continuous passive motion compared with no prophylaxis, the outcome DVT was reported in one study. There was no clinical difference for this outcome, however it was associated with considerable uncertainty. The quality of the evidence was very low due to risk of bias, indirectness and imprecision.

**Network meta-analysis statements**

*DVT (symptomatic and asymptomatic)*

23 studies were included in the network meta-analysis (NMA) for the outcome of DVT (symptomatic and asymptomatic), involving 19 treatments. Treatments included no VTE prophylaxis, pharmacological and mechanical interventions as single agents as well as combination interventions of both pharmacological and mechanical interventions. Results from the network meta-analysis presented rivaroxaban, apixaban and LMWH at a high dose for a standard duration as the most clinically effective interventions in terms of DVT (symptomatic and asymptomatic). The least clinically effective interventions were no prophylaxis, AES (length unspecified) and LMWH at a high dose for a standard duration in combination with AES (length unspecified). Three inconsistencies were identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a fair amount of uncertainty around the rank-point estimates with very wide credible intervals.

*PE*

12 studies were included in the NMA for the outcome of PE, involving 13 treatments. Treatments included no VTE prophylaxis, pharmacological and mechanical interventions as single agents as well as combination interventions of both pharmacological and mechanical interventions. Results from the network meta-analysis presented LMWH at a standard dose for an extended duration, rivaroxaban and IPCD (length unspecified) as the most clinically effective interventions in terms of the outcome of PE. The least clinically effective interventions were UFH, LMWH at a standard dose for standard duration in combination with AES and no prophylaxis. No inconsistencies were identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a high amount of uncertainty around the rank-point estimates with very wide credible intervals.

*Major bleeding*

19 studies were included in the NMA for the outcome of major bleeding, involving 11 treatments. Treatments included no VTE prophylaxis and pharmacological interventions (mechanical interventions were combined with no prophylaxis as the assumption was made that these interventions do not contribute to bleeding risk). Results from the network meta-analysis presented LMWH at a low dose for a standard duration, LMWH at a standard dose for an extended duration,

and VKA as the most clinically effective interventions in terms of the outcome of major bleeding. The least clinically effective interventions were fondaparinux, rivaroxaban and LMWH at a standard dose for a standard duration. No inconsistencies were identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a high amount of uncertainty around the rank-point estimates with very wide credible intervals.

**Economic**

- One original cost-utility analysis found that, in people admitted for elective knee replacement surgery, the following interventions were cost-effective (having positive incremental net monetary benefit [INMB]) compared to LMWH (standard dose, standard duration) +AEs: Foot pump (INMB £353), aspirin (INMB £281), foot pump+ AES (INMB £72). This analysis was assessed as directly applicable with potentially serious limitations.

## 27.6 Recommendations and link to evidence

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| **Recommendations** | **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:**<br>• **aspirin[n] (75 or 150 mg) for 14 days**<br>• **LMWH[o] for 14 days combined with anti-embolism stockings until discharge**<br>• **Rivaroxaban[p]. 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]**<br><br>**1.5.12 Consider one of the following if none of the options in recommendation 1.5.11 can be used:**<br>• **Apixaban[q] is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement** |

n 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.

o 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.

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.

q 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

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| | **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).]**<br>• **Dabigatran etexilate[r], 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).]**<br><br>**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]** |
| **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), fatal PE (7-90 days from hospital discharge), major bleeding (up to 45 days from hospital discharge) and surgical site haematoma (up to 45 days from hospital discharge) as critical outcomes.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) and infection (duration of study) as important outcomes.<br>Three network meta-analyses were conducted for this population, evaluating the outcomes DVT (symptomatic and asymptomatic), PE and major bleeding across numerous interventions.<br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Evidence from direct pairwise comparisons was included in the network meta-analyses for the elective knee replacement population. The quality of the pairwise comparisons ranged from very low to high due to risk of bias, imprecision, indirectness and inconsistency.<br>The DVT (symptomatic and asymptomatic) network evaluated 19 interventions, the PE network evaluated 13 interventions and major bleeding network evaluated 11 interventions. Inconsistencies were identified in the DVT (symptomatic and asymptomatic) and PE networks between the direct pairwise evidence and the NMA evidence but there was good calibration for all the outcomes with small differences between the residual deviance and DIC values for the network meta-analysis models that were ran. Very wide credible intervals around the median network meta-analyses values present some uncertainty around the NMA results, particularly for |

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

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.

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| | the PE and major bleeding networks. |
| Trade-off between clinical benefits and harms | The clinical evidence presented to the committee and orthopaedic subgroup informed the economic model that was developed. The committee's discussions on the clinical evidence guided the recommendations alongside discussions on the results of the economic model. The model evaluated cost effectiveness using clinical data from the network-meta analyses undertaken on the committee-specified critical outcomes of DVT (symptomatic and asymptomatic), PE, and major bleeding. The model also captured data from the included trials on additional outcomes such as symptomatic DVT and asymptomatic DVT, and more detailed bleeding outcomes such as surgical site bleeding, gastrointestinal bleeding, and wound haematoma.<br><br>When assessing the results of the analysis of the clinical data, the committee noted the wide credible intervals presented in the network meta-analyses, particularly in the PE and major bleeding networks, and that the uncertainty in the clinical data would have a knock on effect for the certainty in the results of the economic modelling.<br><br>The licenced DOACs (rivaroxaban, apixaban and dabigatran) ranked highly when considering the clinical data for DVT, with rivaroxaban and apixaban ranked as the top two interventions having relatively narrow credible intervals. Based on the point estimates in the ranking, rivaroxaban (for 14 days) also outperformed dabigatran and apixaban in the analysis of the clinical data for PE. However there was considerable overlap of the confidence intervals for all of the DOACs due to the large uncertainty around the ranking results. None of the DOACs performed as well with respect to major bleeding.<br><br>The committee and orthopaedic subgroup noted that the network meta-analyses suggest that combination prophylaxis may not be highly beneficial, but acknowledged that there is a lot of uncertainty as indicated by the wide credible intervals. The orthopaedic subgroup discussed that the use of AES is common within clinical practice in the eTKR population, without any presence of clinical benefit, with AES showing low rankings in preventing VTE outcomes (DVT and PE). It was discussed whether mechanical prophylaxis may be used due to pharmacological contraindications, and if clinicians might consider IPCD as the intervention of choice as there is a suggested clinical benefit of these interventions in terms of DVT (symptomatic and asymptomatic) and PE, with some uncertainty. The ranking for foot pump based on the clinical data was relatively high in the DVT NMA but it was discussed that the study which influenced the rank of this intervention was conducted during a time period when clinical practice was very different. Foot pumps are not commonly used by people undergoing elective knee replacement surgery for very long in the post-operative period due to the fact that this device can limit early mobilisation.<br><br>The inclusion of aspirin and LMWH combined with anti-embolism stockings (until discharge) in the recommendation was primarily based on the results from the economic model (see 'Trade-off between net clinical effects and costs' section for further discussion). The duration of the interventions were based on the durations presented in the relevant clinical trials. |
| Trade-off between net clinical effects and costs | An original economic model was developed to assess the cost effectiveness of the prophylaxis options included in the clinical review NMAs. It models the outcomes from the NMAs and also differentiates between asymptomatic and symptomatic DVT. This takes into account that asymptomatic DVT does not have an impact on costs and outcomes in the short term as it is not diagnosed in practice and its only consequence in the model is its future progression to PTS.<br><br>Thirteen options were included in this model:<br>• Anti-embolism stockings (AES ) – length unspecified<br>• Aspirin<br>• Apixaban |

- Dabigatran
- Fondaparinux+ AES
- Foot pump
- Foot pump + AES
- IPCD
- LMWH (standard dose, standard duration)
- LMWH (standard dose, extended duration)
- LMWH (standard dose, standard duration) + Anti-embolism stockings (AEs)
- No prophylaxis
- Rivaroxaban

The model results showed that the most cost-effective option for this population is foot pump. This intervention had the highest mean incremental net monetary benefit (INMB) per patient compared to LMWH (standard dose, standard duration) + anti-embolism stockings (£353) at a cost-effectiveness threshold of £20,000 per QALY gained. It was followed by aspirin with INMB of £281. Compared to no prophylaxis, all options ranked higher, except dabigatran. A number of sensitivity analyses were presented to the committee including changing the cost-effectiveness threshold to £30,000 per QALY gained; changing the discount rate for costs and QALYs to 1.5%; and using the licensed duration where applicable rather than the average RCT duration.

The committee and the orthopaedic subgroup considered the results of the model and noted that there was considerable uncertainty in this analysis which is likely to be the result of the uncertainty in the NMAs that informed the model; particularly the PE NMA, where the results were very imprecise. However, the results overall suggested that low-intensity, single-component and low-cost interventions are the most likely to be cost-effective in this population, with foot pump and aspirin ranking first and second. This was thought to be a result of the lower PE and symptomatic DVT incidence in the modelled cohort for the eTKR population compared to the eTHR population.

The committee and the orthopaedic subgroup noted that despite being the most cost-effective option, foot pump had a low probability of being the most cost-effective (18%). This further emphasised the fact that considerable uncertainty exists in the analysis, which was also reflected in the very wide 95% CIs around the mean ranks. Hence, the committee opted to give a choice of prophylaxis options, noting that some people may have contraindications.

The committee and the orthopaedic subgroup noted that out of the three DOACs included in the model (rivaroxaban, apixaban and dabigatran), rivaroxaban was dominant (more effective and less costly) compared to both apixaban and dabigatran. The committee noted that this was in line with previously published economic evaluations, the economic models assessed as part of TA170 and TA245 and a more recent analysis funded by the NIHR.[229,230,281] Dabigatran was also, on average, worse than no prophylaxis. The orthopaedic subgroup also noted recent reports of increased risk of wound complications and subsequent increased length of hospital stay when using dabigatran.[35] The committee noted that despite being dominated and having low INMB, apixaban had high probability of being the most cost-effective (43%). However, there was higher uncertainty around its cost-effectiveness; with around 5% probability of being the worst (compared to 0% for rivaroxaban) and 95% CI around its mean rank of 1 to 13 (compared to 1 to 11 for rivaroxaban). Hence, the committee recommended rivaroxaban as the most cost-effective DOAC with the aim of standardising practice to minimise costs and reduce errors. Apixaban and dabigatran already have current technology appraisal guidance associated with them and are, therefore, also recommended. However, as both were not cost effective compared to rivaroxaban, the committee decided that these

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| | options could only be considered if all the three recommended options are not suitable for the person (for example due to contraindications or issues related to patient preference).<br><br>For those with contraindications for pharmacological prophylaxis, the committee and the orthopaedic subgroup considered that foot pump/IPCD appeared to be more cost-effective in this population compared to AES. This was in line with the evidence from other populations where AES tended to be less effective than previously thought. The committee also noted the difficulty in using AES in this specific population where application is only possible on the opposite leg. Given the very large cost impact of using AES in this population, the considerable time required for nurses to fit them and the considerable uncertainty about their effectiveness; the committee and the subgroup considered that the use of AES as a sole prophylaxis option in this population should be discouraged. However, AES still ranked higher than no prophylaxis and the committee therefore determined there was not enough evidence to recommend against their use as a sole means of prophylaxis.<br><br>The committee also noted that in general it was not possible to include any side effects for the mechanical prophylaxis options in the model, and hence their cost effectiveness might be over-estimated. Additionally, the trials of all mechanical prophylaxis options have used them for longer durations than how they are currently used in practice, where early mobilisation is encouraged, so the efficacy levels seen in the trials may not be possible to replicate in practice. Hence, a weaker “consider” recommendation would be more appropriate. |
| Other considerations | The committee noted 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. |

# 28 Non-arthroplasty orthopaedic knee surgery

## 28.1 Introduction

Non-arthroplasty knee surgery can include knee arthroscopy, osteotomy and surgery for peri-articular trauma. This population was previously covered in the 'other orthopaedic surgery' chapter in CG92. The number of non-arthroplasty knee surgeries performed has increased over the years, therefore it is important that this population is evaluated separately. These surgeries are commonly performed in relatively younger patients and may not be extensive. They are associated with a lower VTE risk compared with elective total knee replacement, possibly due to the shorter surgery duration and earlier mobilisation of patients.

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

For full details see review protocol in appendix C.

**Table 121: PICO characteristics of review question**

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| **Population** | Adults and young people (16 years and older) having non-arthroplasty knee surgery who are:<br>• Admitted to hospital<br>• Having day procedures<br>• Outpatients post-discharge |
| **Interventions** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to |

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| | maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300mg)*<br><br>*off-label |
| **Comparisons** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study) |

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| | • Unplanned return to theatre (up to 45 days from hospital discharge) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs |
| **Stratification** | • People who are contraindicated for pharmacological prophylaxis<br>• People who are contraindicated for mechanical prophylaxis<br>• Major arthroscopic surgery (combined anaesthetic and surgery longer than 1 hour)<br>• Minor arthroscopic surgery (combined anaesthetic and surgery less than 1 hour)<br>• Osteotomy<br>• Peri-articular trauma |

## 28.3 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of mechanical and pharmacological prophylaxis strategies (alone or in combination) in people with non-arthroplasty knee surgery. Five studies were included in the review;[45 ,46 ,203 ,301 ,319] these are summarised in Table 122 below. Of the four studies included in the previous guideline (CG92), three were included [46 ,203 ,319], and one was excluded due to the intervention arm including both low and standard doses of LMWH.[213] Two new studies were identified for inclusion for this update. [301, 45] Evidence from these studies is summarised in the clinical evidence summary below (Table 123, Table 124,Table 125, Table 126, Table 127, Table 128, Table 129). 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.

The five included studies all included an arthroscopy surgery population. Although other types of non-arthroplasty knee surgery were searched for, including osteotomy, fracture surgery and peri-articular trauma, no studies involving these populations were identified for inclusion in this review.

As per the review protocol, studies were stratified according to the population. As a result, three strata exist in the current review. The major arthroscopic surgery stratum includes studies where the population had a mean combined anaesthetic and surgery time of over 1 hour. The minor arthroscopic surgery stratum includes studies where the population had a mean combined anaesthetic and surgery time of less than 1 hour. The overall population stratum includes studies where combined anaesthetic and surgery time was not sufficiently reported. The included studies did not report on the other specified stratification populations and therefore no other strata are included.

**Table 122: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| **Overall population stratum** | | | | |
| Camporese 2008[46] | Intervention 1 (n=660): AES, full length<br>Applied to the operated leg before weight bearing, and worn for 7 days<br><br>Intervention 2 (n=444): LMWH, high dose, extended duration (nadroparin, | n=1761<br><br>People having diagnostic arthroscopy or arthroscopy assisted knee surgery<br><br>Duration of operation not reported (overall strata)<br><br>Males and females: AES | All-cause mortality (8 days)<br><br>DVT (8 days): confirmed by ultrasonography<br><br>PE (8 days): confirmed by ventilation perfusion lung scan | |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | 3800U, once daily)<br>Administered 8 hours after procedure, for 14 days<br><br>Comparison (n=657): LMWH, high dose, standard duration (nadroparin, 3800U, once daily)<br>Administered 8 hours after procedure, for 7 days | group 1.66:1, LMWH extended group 1.60:1, LMWH standard group 1.62:1<br><br>Italy | Major bleeding (8 days): defined as a clinically overt haemorrhage associated with a haemoglobin decrease of at least 20g/L or requiring transfusion of 2 or more units of packed red blood cells, a retroperitoneal or intracranial event, a bleeding event requiring reintervention or a hemarthrosis with joint drainage of more than 450ml. | |
| Camporese 2016[45] | Intervention (n=122): Rivaroxaban (10mg, once daily)<br><br>Comparison (n=119): no VTE prophylaxis (placebo)<br><br>Started 8-10 hours postoperatively, for 6 days | n=241<br><br>People having non-diagnostic arthroscopy assisted knee surgery<br><br>Duration of operation and/or anaesthesia not reported<br><br>Age >18 years<br><br>Males and females (162:79)<br><br>Italy | All-cause mortality (90 days)<br><br>DVT (90 days): confirmed by Doppler ultrasonography<br><br>PE (90 days): confirmed by CT angiography<br><br>Fatal PE (90 days): confirmed by autopsy, or on clinical grounds according to the treating physician | |
| Marlovits 2007[203] | Intervention (n=87): LMWH, standard dose, extended duration (enoxaparin, 40mg, once daily)<br>Administered 12-18 hours preoperatively and continued for 23-28 days<br><br>Comparison (n=88): LMWH, standard dose, standard duration (enoxaparin, 40mg, once daily) | n=175<br><br>People having arthroscopic anterior cruciate ligament (ACL) surgery<br><br>Duration of operation >2 hours: 50%<br><br>Age >19 years<br>Males and females (108:67) | DVT (23-28 days): confirmed by magnetic resonance venography<br><br>PE (23-28 days): confirmed by lung scan<br><br>Major bleeding (23-28 days): defined as fatal bleeding, bleeding that was retroperitoneal, intracranial, | |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Administered 12-18 hours preoperatively and continued for 3-8 days plus placebo for the following 20 days | Austria | intraspinal or involving any critical organ, bleeding leading to reoperation, transfusion of 2 units of packed red blood cells or whole blood, or overt bleeding with a bleeding index of 2 or more | |
| **Major arthroscopic surgery stratum** | | | | |
| Wirth 2001[319] | Intervention (n=117): LMWH, low dose (reviparin, 1750U, once daily)<br><br>Comparison (n=122): no VTE prophylaxis | n=239<br><br>People having diagnostic arthroscopy or arthroscopy assisted knee surgery<br><br>Duration of surgery (mean, SD): 34 (38) minutes<br>Duration of anaesthesia (mean, SD): 68 (46) minutes<br><br>Age >18 years<br>Males and Females (179:60)<br><br>Germany | DVT (10 days): confirmed by compression ultrasonography<br><br>PE (10 days): confirmed by compression ultrasonography<br><br>Major bleeding (10 days): defined as transfusion or reoperation due to bleeding<br><br>Clinically relevant non-major bleeding (10 days): defined as wound haematoma (>2cm and <2cm) | Duration of anaesthesia SD is very wide so may have been less than 1 hour for many patients |
| **Minor arthroscopic surgery stratum** | | | | |
| Van Adrichem 2017[301] | Intervention (n=773): LMWH, low dose (nadroparin 2850U or dalteparin 2500U, once daily)<br>Administered for 8 days post operatively<br><br>Comparison (n=770): no VTE prophylaxis | n=1543<br><br>People having meniscectomy, diagnostic arthroscopy or removal of corpora libera<br>(meniscectomy 72.5%, removal of loose bodies 5.3%, diagnostic arthroscopy 7.4%, other 22%)<br><br>Total duration (time from receiving anaesthesia to leaving operating room): LMWH group, 26 (11) minutes; control group, 26 (11) minutes | All-cause mortality (90 days)<br><br>PE (90 days): method of confirmation not reported | Type of LMWH was dependent on hospital preference<br><br>If the patient's weight is more than 100kg a double dose of LMWH was given |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | Age >18 years<br>Males and females (810: 733)<br><br>Netherlands | | |

### 28.3.1 Pairwise comparisons: overall population stratum

**Table 123: 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 | Risk difference with LMWH (standard dose, extended duration) (95% CI) |
| DVT | 140<br>(1 study)<br>23-28 days | MODERATE[a]<br>due to risk of bias | RR 0.07<br>(0.02 to 0.27) | 412 per 1000 | 383 fewer per 1000<br>(from 301 fewer to 404 fewer) |
| PE | 140<br>(1 study)<br>23-28 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 28 fewer to 28 more)[d] |
| Major bleeding | 140<br>(1 study)<br>23-28 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 28 fewer to 28 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 Could not be calculated as there were no events in the intervention or comparison group

d Risk difference calculated in Review Manager

**Table 124: Clinical evidence summary: LMWH (high dose, standard duration) versus AES (full length)**

| Outcomes | No of Participants | Quality of the | Relative effect | Anticipated absolute effects |
|---|---|---|---|---|

| | (studies) Follow up | evidence (GRADE) | (95% CI) | Risk with AES | Risk difference with LMWH (95% CI) |
|---|---|---|---|---|---|
| All-cause mortality | 1317<br>(1 study)<br>8 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 3 fewer to 3 more)[d] |
| DVT | 1317<br>(1 study)<br>8 days | MODERATE[a]<br>due to risk of bias | RR 0.35<br>(0.17 to 0.70) | 44 per 1000 | 29 fewer per 1000<br>(from 13 fewer to 36 fewer) |
| PE | 1317<br>(1 study)<br>8 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 1.00<br>(0.14 to 7.15) | 3 per 1000 | 0 fewer per 1000<br>(from 3 fewer to 18 more) |
| Major bleeding | 1317<br>(1 study)<br>8 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 1.96<br>(0.20 to 18.86) | 2 per 1000 | 1 more per 1000<br>(from 1 fewer to 26 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 125: Clinical evidence summary: LMWH (high dose, extended duration) versus AES (full length)**

| 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) |
| All-cause mortality | 1104<br>(1 study)<br>8 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 4 fewer to 4 more)[d] |
| DVT | 1104<br>(1 study) | LOW[a,b] | RR 0.46<br>(0.22 to 0.97) | 44 per 1000 | 24 fewer per 1000<br>(from 1 fewer to 34 fewer) |

| 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) |
| | 8 days | due to risk of bias, imprecision | | | |
| PE | 1104 (1 study) 8 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.50 (0.20 to 11.13) | 3 per 1000 | 2 more per 1000 (from 2 fewer to 30 more) |
| Major bleeding | 1104 (1 study) 8 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.50 (0.09 to 25.41) | 2 per 1000 | 1 more per 1000 (from 1 fewer to 36 more) |

1 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

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

3 Could not be calculated as there were no events in the intervention or comparison group

4 Risk difference calculated in Review Manager

**Table 126: 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 | Risk difference with LMWH (high dose, extended duration) (95% CI) |
| All-cause mortality | 1101 (1 study) 8 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 4 fewer to 4 more)[d] |
| DVT | 1101 (1 study) 8 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.33 (0.55 to 3.25) | 15 per 1000 | 5 more per 1000 (from 7 fewer to 34 more) |
| PE | 1101 | | Peto OR 1.5 | 3 per 1000 | 2 more per 1000 |

| 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 LMWH (high dose, extended duration) (95% CI) |
| | (1 study)<br>8 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | (0.2 to 11.06) | | (from 2 fewer to 30 more) |
| Major bleeding | 1101<br>(1 study)<br>8 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.75<br>(0.07 to 7.52) | 3 per 1000 | 1 fewer per 1000<br>(from 3 fewer to 19 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 127: Clinical evidence summary: Rivaroxaban versus no 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 Rivaroxaban versus no prophylaxis (95% CI) |
| All-cause mortality | 234<br>(1 study)<br>90 days | LOW[a]<br>due to imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000<br>(from 17 fewer to 17 more)[c] |
| DVT | 234<br>(1 study)<br>90 days | MODERATE[a]<br>due to imprecision | RR 0.24<br>(0.05 to 1.09) | 70 per 1000 | 53 fewer per 1000<br>(from 67 fewer to 6 more) |
| PE | 234<br>(1 study)<br>90 days | LOW[a]<br>due to imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000<br>(from 17 fewer to 17 more)[c] |

| 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 Rivaroxaban versus no prophylaxis (95% CI) |
| Fatal PE | 234 (1 study) 90 days | LOW[a] due to imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000 (from 17 fewer to 17 more)[c] |

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b Could not be calculated as there were no events in the intervention or comparison group
c Risk difference calculated in Review Manager

### 28.3.2 Pairwise comparisons: Major arthroscopic surgery stratum

**Table 128: 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) |
| DVT | 239 (1 study) 10 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.27 (0.05 to 1.35) | 41 per 1000 | 30 fewer per 1000 (from 39 fewer to 14 more) |
| PE | 239 (1 study) 10 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 16 fewer to 16 more)[d] |
| Major bleeding | 239 (1 study) 10 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 16 fewer to 16 more)[d] |
| CRNMB | 239 (1 study) 10 days | LOW[a,b] due to risk of bias, imprecision | Peto OR 0.31 (0.05 to 1.80) | 33 per 1000 | 22 fewer per 1000 (from 31 fewer to 25 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 (low 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<br>b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs<br>c Could not be calculated as there were no events in the intervention or comparison group<br>d Risk difference calculated in Review Manager | | | | | |

### 28.3.3 Pairwise comparisons: Minor arthroscopic surgery stratum

**Table 129: 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) |
| All-cause mortality | 1451<br>(1 study)<br>90 days | LOW[a]<br>due to imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 3 fewer to 3 more)[d] |
| PE | 1451<br>(1 study)<br>90 days | VERY LOW[a,b]<br>due to indirectness, imprecision | Peto OR 0.98<br>(0.06 to 15.76) | 1 per 1000 | 0 fewer per 1000<br>(from 1 fewer to 20 more) |
| a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs<br>b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol<br>c Could not be calculated as there were no events in the intervention or comparison group<br>d Risk difference calculated in Review Manager | | | | | |

## 28.4 Economic evidence

No relevant health economic studies were identified.

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

## 28.5 Evidence statements

### 28.5.1 Clinical

#### LMWH compared with no prophylaxis

In the major arthroscopic surgery stratum, one study compared LMWH at a low dose with no prophylaxis. The evidence suggested clinical benefit of LMWH for both DVT and clinically relevant non-major bleeding (low to very low quality, n=239), but no clinical difference in terms of PE or major bleeding (very low quality, n=239), however there was considerable uncertainty around these results.

Evidence from a single study in the minor arthroscopic surgery stratum demonstrated no clinical difference between treatments in terms of all-cause mortality and PE (very low to low quality, n=1451), although the uncertainty around these results could also have been associated with both benefit and harm.

#### LMWH compared with AES

In the overall population stratum, evidence from a single study suggested that LMWH at a high dose and standard duration had no clinically important benefit over AES (full length) in terms of all-cause mortality or PE (very low quality, n=1317). In terms of DVT, evidence suggested a clinical benefit of LMWH compared to AES, however there was a possible clinical harm of LMWH in terms of major bleeding (very low to moderate quality, n=1317). However all of the results were associated with considerable uncertainty.

When LMWH at a high dose and extended duration was compared to AES (full length) in a single study in the overall population stratum, there was no clinical difference between treatments in terms of all-cause mortality. The evidence suggested a clinical benefit of LMWH in terms of DVT, however there was a possible clinical harm of LMWH compared to AES in terms of both PE and major bleeding (low to very low quality, n=1104). However all of the results were associated with considerable uncertainty.

#### LMWH extended duration compared with LMWH standard duration

In the overall population stratum, a single study (n=140) compared LMWH at a standard dose and extended duration to LMWH at a standard dose and standard duration. Evidence from this study demonstrated a clinical benefit for extended duration LMWH in terms of DVT (moderate quality), and suggested no clinical difference was seen for PE or major bleeding. However there was very serious imprecision associated with the PE and major bleeding outcomes.

In the overall population, LMWH at a high dose and extended duration was compared to LMWH at a high dose and standard duration, in a single study (n=1101). No clinical difference was seen between the treatments in terms of all-cause mortality and major bleeding, however there was a possible clinical harm of extended duration LMWH in terms of DVT and PE (very low quality). However there was very serious imprecision associated with all these results.

**Rivaroxaban versus no prophylaxis**

In the overall population stratum, a single study (n=234) compared rivaroxaban with no prophylaxis. Evidence from this study suggested a clinical benefit in terms of DVT for rivaroxaban, however there was no clinical difference between treatments in terms of all-cause mortality, PE and fatal PE (low to moderate quality) and there was considerable uncertainty around these results.

**Economic**

- No relevant economic evaluations were identified.

## 28.6 Recommendations and link to evidence

| | |
|---|---|
| **Recommendations** | **1.5.14 Be aware that VTE prophylaxis is generally not needed for people undergoing arthroscopic knee surgery where:**<br>• **total anaesthesia time is less than 90 minutes and**<br>• **the person is at low risk of VTE. [2018]**<br><br>**1.5.15 Consider LMWH[s] 6–12 hours after surgery for 14 days for people undergoing arthroscopic knee surgery if:**<br>• **total anaesthesia time is more than 90 minutes or**<br>• **the person's risk of VTE outweighs their risk of bleeding. [2018]**<br><br>**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]** |
| **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.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Five studies were included in this review. Three of these were randomised controlled trials identified from the previous guideline (CG92). One study that was included in CG92 was excluded from this review due to the intervention arm including both low and standard doses of LMWH.<br>Seven comparisons were included in the three strata: five in the overall population strata and one each in the major arthroscopic surgery and minor arthroscopic |

[s] 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.

| | |
|---|---|
| | surgery strata. The comparisons evaluated both pharmacological and mechanical interventions. Pharmacological interventions included LMWH (at low, standard and high doses and standard and extended durations) and rivaroxaban. The committee noted that there was no evidence for UFH or other types of pharmacological prophylaxis. The only mechanical intervention was AES (full length). No evidence for other mechanical interventions was identified.<br><br>All of the evidence in this review had a GRADE quality rating that ranged from very low to moderate. This was due to inadequate outcome reporting, lack of allocation concealment, lack of adequate blinding and sequence generation, and high dropout rates, resulting in a high risk of bias rating. Additionally, the majority of the evidence had serious or very serious imprecision, which further downgraded the quality of the evidence. Evidence for the PE and DVT outcomes in the minor arthroscopic stratum was also downgraded due to indirectness, which also reduced the quality rating. This was because the method of confirmation of PE and DVT was not reported. The committee noted the poor quality of the evidence and also that for each comparison there was only one study, therefore limiting the confidence that could be put in the findings. |
| Trade-off between clinical benefits and harms | The committee noted that all studies included in the review all involved an arthroscopy procedure. Although other types of non-arthroplasty knee surgery were searched for, including osteotomy and fractures, no relevant RCTs that could be included were identified. Therefore, the committee made recommendations in terms of the population in the evidence presented and other knee surgery. The duration of LMWH (14 days) was extrapolated from the total knee replacement surgery population.<br><br>The committee discussed that although the studies included in the review were all arthroscopy related procedures, there was great variation in the types of arthroscopic operations, which differ substantially in terms of surgery and immobilisation time, and complexity of the procedure. For instance, it was noted that a diagnostic arthroscopy would be a much quicker and less complex procedure compared to other forms of non-arthroplasty knee surgery.<br><br>The committee also noted that although the study included in the major arthroscopic surgery stratum reported a mean anaesthetic time of over 90 minutes, there was some concern that many of the patients in the study may have had surgery for less than 90 minutes, given the large standard deviation and the type of surgery patients received. The committee noted their concern and took this into account when considering the evidence and recommendations.<br><br>The orthopaedic subgroup advised the committee that the risk of VTE will be minimal if the surgery total anaesthesia time is less than 90 minutes and the individuals undergoing the surgery have been assessed to be at low risk of VTE.<br><br>The committee discussed the increased risk of VTE events if the surgery is performed under general anaesthesia and the total time is more than 90 minutes. It was agreed that in this group prophylaxis needs to be considered based on individual VTE and bleeding risk assessment. |
| Trade-off between net clinical effects and costs | No relevant economic studies were identified for this population and no studies were previously included in CG92. Relevant unit costs were presented to the committee.<br><br>The committee, on the advice of the orthopaedic subgroup, determined that people undergoing non-arthroplasty procedures are generally at low risk of VTE. Factors that contribute to increasing the risk were reported to include the use of general anaesthesia and surgery time. Only in these circumstances will the risk of VTE be high enough to justify the use of the prophylaxis. The committee considered that LMWH was the prophylaxis option supported by the presented clinical evidence. This was also reported to be in line with current practice. Although rivaroxaban showed clinical benefit for the outcome of DVT when compared to no prophylaxis, it was |

| | |
|---|---|
| | acknowledged that it is not licensed for use in this population. Overall, the committee considered that the provision of prophylaxis in this population should be based on individual VTE and bleeding risk assessment to ensure adequate targeting of those most likely to benefit and, hence, justify its cost. |
| Other considerations | None. |

# 29 Foot and ankle orthopaedic surgery

## 29.1 Introduction

The risk of VTE in the foot and ankle surgery population is heterogeneous. However, there are several known risk factors that can increase the risk of VTE, including type and duration of surgery and period of immobilisation. Some patients who have foot or ankle surgery may be immobilised and require the use of a plaster cast or orthosis; these patients are evaluated in the lower limb immobilisation review (chapter 24). This guidance is for the totality of patients treated with lower limb immobilisation; clinicians should consider individual patient risk, such as people with tendoachilles rupture, when determining which VTE prophylaxis intervention is appropriate for a patient.

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

For full details see review protocol in appendix C.

**Table 130: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) having foot and ankle surgery who are:<br>• Admitted to hospital<br>• Having day procedures<br>• Outpatients post-discharge |
| **Interventions** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to |

| | |
|---|---|
| | maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300mg)*<br><br>*off-label |
| **Comparisons** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Unplanned return to theatre (up to 45 days from hospital discharge) |

| Study design | Randomised controlled trials (RCTs), systematic reviews of RCTs |
|---|---|

## 29.3 Clinical evidence

No relevant clinical studies comparing different pharmacological and mechanical prophylaxis strategies for people who are undergoing foot and ankle surgery were identified. See the study selection flow chart in appendix E and excluded studies list in appendix N.

## 29.4 Economic evidence

### Published literature

No relevant health economic studies were identified.

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

## 29.5 Evidence statements

### Clinical

No relevant clinical studies were identified.

### Economic

No relevant economic evaluations were identified.

## 29.6 Recommendations and link to evidence

| **Recommendations** | **1.5.17 Consider pharmacological VTE prophylaxis for people undergoing foot or ankle surgery:**<br>• **that requires immobilisation (for example, arthrodesis or arthroplasty). Consider stopping prophylaxis if immobilisation continues beyond 42 days (see recommendation 1.5.4) or**<br>• **when total anaesthesia time is more than 90 minutes or**<br>• **the person's risk of VTE outweighs their risk of bleeding. [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.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br>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 clinical evidence was identified for inclusion in this review. |
| Trade-off between clinical benefits and harms | In the absence of any clinical evidence, the committee considered advice from the orthopaedic subgroup and discussed that for those undergoing foot and ankle surgery, prophylaxis is not indicated for those whose surgery lasts less than 90 minutes, are not subsequently immobilised and are assessed as low risk for VTE.<br>Where patients are immobilised after their foot or ankle surgery the risk of VTE is the same as the population reviewed for lower limb immobilisation and therefore the same recommendations apply, including the consideration of stopping prophylaxis if immobilisation continues after 42 days. |
| Trade-off between net clinical effects and costs | No relevant economic studies were identified for this population. Relevant unit costs were presented to the committee.<br>The committee acknowledged that the risk of VTE will be minimal if the surgery total anaesthesia time is less than 90 minutes and the person undergoing the surgery has been assessed to be at low risk of VTE. This means that provision of prophylaxis for this group is unlikely to be cost-effective. Where immobilisation is required the risk of VTE will be higher, which would justify the cost of provision of prophylaxis. For this group, LMWH has been recommended based on the evidence considered specifically for people discharged with lower limb immobilisation in a separate chapter in this update. This was also reported to be in line with current practice. The committee acknowledged that long durations of immobilisation in this population are unlikely; however, the decision to continue prophylaxis beyond 6 weeks (42 days) should be made based on the balance between VTE and bleeding risks. |
| Other considerations | The ‘consider’ recommendation is a reflection of the lack of evidence in this population. However, it is the committee’s view that for this group of patients, prophylaxis is likely to be most clinically and cost effective when immobilisation is required or anaesthesia time is longer than one hour.<br>The committee noted that not all patients who receive lower limb immobilisation are orthopaedic patients; for example, some patients with diabetic foot also receive immobilisation. This group of patients is also included in these recommendations. |

# 30 Upper limb orthopaedic surgery

## 30.1 Introduction

It has been reported that over 4,000 shoulder and elbow replacements are performed in the UK each year. The risk of VTE in this population is thought to be very low. However, there are some known risk factors associated with upper limb surgery that can increase the risk of VTE. Similar to some other surgical populations, the two main risk factors are duration of surgery and use of general anaesthesia.

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

For full details see review protocol in appendix C.

**Table 131: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) having upper limb surgery who are:<br>• Admitted to hospital<br>• Having day procedures<br>• Outpatients post-discharge |
| **Interventions** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only) |

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| | ○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300mg)*<br><br>*off-label |
| **Comparisons** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Unplanned return to theatre (up to 45 days from hospital discharge)<br>• Upper limb DVT (7-90 days from hospital discharge. Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs |

## 30.3 Clinical evidence

No relevant clinical studies comparing difference pharmacological and mechanical prophylaxis strategies for people who are undergoing upper limb surgery. See the study selection flow chart in appendix E and excluded studies list in appendix N.

## 30.4 Economic evidence

**Published literature**

No relevant health economic studies were identified.

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

## 30.5 Evidence statements

**Clinical**

No relevant clinical studies were identified.

**Economic**

No relevant economic evaluations were identified.

## 30.6 Recommendations and link to evidence

| **Recommendations** | **1.5.18 Be aware that VTE prophylaxis is generally not needed if giving local or regional anaesthetic for upper limb surgery. [2018]**<br><br>**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]** |
|---|---|
| **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.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br>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 clinical evidence was identified for this review. |
| Trade-off between | The committee acknowledged that the risk of VTE is minimal in this population, |

| | |
|---|---|
| clinical benefits and harms | particularly if the surgery is performed under local anaesthetic and the person undergoing the surgery has been assessed to be at low risk of VTE.<br>The committee discussed that the increased risk of VTE events for people undergoing upper limb surgery is associated with surgery with a total general anaesthetic time over 90 minutes. The committee noted that this 90 minutes time-point is longer than the minimum time-point recommended for consideration of VTE prophylaxis in the lower limb surgery populations (60 minutes). This is due to the lower risk of developing VTE in upper limb surgeries compared to that of lower limb surgeries.<br>In this group, the committee view was that prophylaxis should be considered based on individual VTE and bleeding risk assessment. |
| Trade-off between net clinical effects and costs | No relevant economic studies were identified for this population. Unit costs were presented to the committee.<br>Given the lack of evidence, the committee considered that the provision of prophylaxis is likely to be cost effective only for individuals at higher risk of VTE where the cost of prophylaxis is likely to be off-set by the cost of averted VTE events. |
| Other considerations | The committee highlighted that some older people use their arms to support mobilisation (for example with a walking stick or frame). Therefore arm surgery would render this population partially immobilised until they recover from the upper limb surgery and their arm is no longer being used to support mobilisation.<br>The 'consider' recommendation is a reflection of the lack of evidence in this population. However, it is the committee's view that for this group of patients, prophylaxis is likely to be most clinically and cost effective when total time under general anaesthesia is longer than 90 minutes. |

# 31 Elective spinal surgery

## 31.1 Introduction

Elective spinal surgery is a subspecialty of both orthopaedic surgery and neurosurgery. It includes acute spinal injury surgery and elective spinal surgery (this evidence review will focus on elective spinal surgery). There is considerable uncertainty about the incidence of VTE events in the spinal surgery population. Despite this uncertainty the impact that a bleeding or VTE event can have is widely appreciated. In particular, the catastrophic long-term neurological consequences of extradural bleeding need to be balanced against the risk to life of VTE. Due to the potentially life-changing effect a bleeding event can have, it is important that the patient process involves the active recording of the clinical decision rather than a passive default position of no treatment.

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

For full details see review protocol in appendix C.

**Table 132: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) undergoing spinal surgery admitted to hospital, having day procedures or outpatients post-discharge |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily) |

| | |
|---|---|
| | • Vitamin K Antagonists:<br>  ○ warfarin (variable dose only)<br>  ○ acenocoumarol (all doses)<br>  ○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (2.5mg twice daily)<br>• Dabigatran (220mg once daily; 150mg once daily - patients with moderate renal impairment, interacting medicines, over 75 years old)<br>• Rivaroxaban (10mg once daily)<br>• Aspirin (up to 300mg)*<br><br>*off-label |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• Pulmonary embolism (symptomatic and asymptomatic) (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<br>• 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 returning to theatre for surgery for control of bleeding<br>• 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<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Unplanned return to theatre (up to 45 days from hospital discharge) |

| Study design | Randomised controlled trials (RCTs), systematic reviews of RCTs. |
|---|---|

## 31.3 Clinical evidence

Two studies were included in the review [81] [322]; these are summarised in Table 133 below. One study was previously included in the previous guideline (CG92), [322] and one study was added in the update.

One study that was previously included in CG92, has been excluded as the outcomes were measured at 5 days (the minimum time-point is 7 days, as reported in the protocol (appendix C) [257].

Evidence from these studies is summarised in the clinical evidence summary below (Table 134 and Table 135). 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 133: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Du 2015[81] | Intervention (n=324):<br>LMWH, parnaparin, 40mg once daily (standard dose), subcutaneously administered from 6-8 hours after surgery for 14 days when patients could fully ambulate.<br><br>Comparison (n=341):<br>Rivaroxaban, 10mg, once daily, orally from 6-8 hours after surgery for 14 days when the patients could fully ambulate. | n=665<br><br>People undergoing lumbar spinal surgery<br><br>Age (mean): ≥60 years, 40% (no further details reported)<br>Gender (male to female ratio): not reported<br><br>China | All-cause mortality (14 days)<br><br>DVT (symptomatic and asymptomatic) (14 days): confirmed by Doppler ultrasonography<br><br>PE (14 days): confirmed by spiral computed tomography (CT) was conducted as soon as possible to determine pulmonary angiography<br><br>Major bleeding (14 days): defined as fatal bleeding, bleeding in inflow critical organs (such as the posterior peritoneum, intracranial, intraocular, and intraspinal canal), bleeding-induced reoperation, or clinically significant bleeding outside the surgical site with a decrease of ≥20 g/L in haemoglobin level | New study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | (with the level from the first postoperative day as the reference value), or the need to transfuse ≥2 units of whole blood or packed red blood cells.<br><br>Clinically relevant non-major bleeding(14 days): included multi-sites bleeding, spontaneous haematoma, big incision haematoma | |
| Wood 1997[322] | Intervention (n=75):<br>Foot pump, inflatable wraps connected through tubing to a pneumatic control unit, inflation <0.4 seconds, cycle repeated every 20 seconds worn during and after surgery until patients were ambulant. Patients also wore AES, thigh-length, until discharge. No details reported about length of stay.<br><br>Comparison (n=59):<br>IPCD, pneumatic compression wrap, thigh-length until patients were ambulant. AES, thigh-length (above-knee), placed on patients shortly before and during surgery and were worn until discharge. No details reported about length of stay. | n=134<br><br>People undergoing spinal surgery, anterior lumbar interbody fusion, posterior lumbar and interbody fusion<br><br>Age (mean): 39.5 years<br>Gender (male to female ratio: 1.4:1<br><br>USA | DVT (symptomatic and asymptomatic) (5-7 days): confirmed by duplex ultrasonography<br><br>PE (5-7 days): definition not reported<br><br>Visual analogue comfort scale (hospital discharge - time-point not reported) | Included in CG92 |

**Table 134: Clinical evidence summary: LMWH (standard dose; standard duration) versus rivaroxaban**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with rivaroxaban | Risk difference with LMWH (standard dose) (95% CI) |
| All-cause mortality | 665 (1 study) 14 days | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 7.79 (0.15 to 392.95) | 0 per 1000 | -[a] |
| DVT (symptomatic and asymptomatic) | 665 (1 study) 14 days | VERY LOW[b,c] due to risk of bias, imprecision | RR 1.4 (0.49 to 4) | 18 per 1000 | 7 more per 1000 (from 9 fewer to 53 more) |
| PE | 665 (1 study) 14 days | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 1.05 (0.07 to 16.88) | 3 per 1000 | 0 more per 1000 (from 3 fewer to 44 more) |
| Major bleeding | 665 (1 study) 14 days | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 0.54 (0.06 to 5.2) | 6 per 1000 | 3 fewer per 1000 (from 6 fewer to 24 more) |
| Clinically relevant non-major bleeding | 665 (1 study) 14 days | VERY LOW[b,c] due to risk of bias, imprecision | RR 1.05 (0.34 to 3.23) | 18 per 1000 | 1 more per 1000 (from 12 fewer to 39 more) |

a Absolute effects could not be calculated due to zero events in the control arm
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 135: Clinical evidence summary: Foot pump + AES (above-knee) versus IPCD (above-knee) + AES (above-knee)**

| Outcomes | No of | Quality of the evidence | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | effect (95% CI) | Risk with IPCD + AES (above-knee) | Risk difference with Foot pump + AES (above-knee) (95% CI) |
|---|---|---|---|---|---|
| DVT (symptomatic and asymptomatic) | 134 (1 study) 5-7 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 30 fewer to 30 more)[d] |
| PE | 134 (1 study) 5-7 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 30 fewer to 30 more)[d] |
| Visual analogue comfort scale Scale from: 0 to 10. | 134 (1 study) Hospital discharge; time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | - | The mean visual analogue comfort scale (hospital discharge) in the control groups was 5.56 | The mean visual analogue comfort scale (hospital discharge) in the intervention groups was 0.28 higher (0.69 lower to 1.25 higher) |

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 Zero events in both arms. Risk difference calculated in Review Manager.

## 31.4 Economic evidence

### Published literature

No relevant health economic studies were identified.

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

## 31.5 Evidence statements

### Clinical

There was possible clinical harm of LMWH in terms of all-cause mortality, DVT (symptomatic and asymptomatic) and possible clinical benefit of LMWH in terms of major bleeding, however there was imprecision around these estimates. There was no clinical difference between LMWH and rivaroxaban in terms of PE and clinically relevant non-major bleeding. Quality of the all evidence in this comparison was very low due to imprecision and indirectness.

There was no clinical difference between foot pump plus AES and IPCD plus AES in terms of DVT (symptomatic and asymptomatic) and PE. There was reported possible clinical harm of foot pump plus AES in terms of the quality of life measure of VAS, however there is uncertainty around this result. Quality of the all evidence in this comparison was very low due to risk of bias, imprecision and indirectness.

### Economic

- No relevant economic evaluations were identified.

## 31.6 Recommendations and link to evidence

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|---|---|
| **Recommendations** | **1.5.20 Offer mechanical VTE prophylaxis on admission to people undergoing elective spinal surgery. Choose either:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression.**<br><br>**Continue for 30 days or until the person is mobile or discharged, whichever is sooner. [2018]**<br><br>**1.5.21 Consider adding pharmacological VTE prophylaxis with LMWH[t] 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** |

[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.

| | |
|---|---|
| | **judgement. [2018]**<br><br>**1.5.22 If using LMWH[u] 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]**<br><br>**1.5.23 If needed, start LMWH[v] 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]** |
| **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.<br>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 thrombocytopaenia (duration of study), technical complications of mechanical interventions (duration of study) and unplanned return to theatre (up to 45 days from hospital discharge) as important outcomes.<br>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 study was previously included in CG92 and the other study was added in the update. The evidence evaluated pharmacological (LMWH and rivaroxaban) and mechanical (foot pump, IPCD and AES) interventions.<br>The comparison of LMWH at a standard dose for a standard duration versus rivaroxaban reported data for all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and clinically relevant non-major bleeding. All of the evidence was graded very low due to risk of bias and imprecision. The comparison of foot pump with AES (above-knee) versus IPCD (above-knee) with AES above-knee) reported outcome data for DVT (symptomatic and asymptomatic), PE and visual analogue comfort scale (VAS). All of the evidence was graded very low due to risk of bias, indirectness and imprecision.<br>The committee noted the lack of evidence for this population and the poor quality of the literature. |
| Trade-off between clinical benefits and harms | The committee discussed that this population is at increased risk due to their high immobility associated with the surgical procedure. With both the induction process and the procedure itself the person is often under general anaesthetic and immobilised for at least 60 minutes. The orthopaedic subgroup and committee discussed that in current practice mechanical interventions are the preferred choice |

[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), 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.

for VTE prophylaxis for spinal surgery patients and LMWH for those patients with a low risk of bleeding. Therefore, it was agreed that a similar prophylaxis strategy as that recommended in CG92 should be adopted; this indicates the use of mechanical VTE prophylaxis from admission for all spinal surgery patients and considering the addition of pharmacological prophylaxis in high VTE risk patients with a low risk of bleeding. Prophylaxis is recommended for 30 days or until the person is mobile or discharged, whichever is sooner. The 30 days is extrapolated from evidence from the stroke population evidence related to the duration of IPC prophylaxis. The committee acknowledge that this may be an arbitrary cut off but wanted to ensure patients do not get prophylaxis for a long period for which there is no evidence to support. Clinicians can reassess a patient's need for prophylaxis if their risk goes on beyond 30 days.

The committee discussed that the results of the comparison between LMWH and rivaroxaban showed little clinical difference between the two interventions in terms of the VTE-related outcomes reported with uncertainty around the results due to imprecision. The committee noted that although rivaroxaban is licensed in other orthopaedic populations (elective hip replacement and elective knee replacement) it is not licensed in a spinal surgery population. LMWH was previously recommended in CG92 and is currently used in standard practice; the committee therefore considered LMWH to be an effective pharmacological intervention to recommend for patients with low risk of bleeding.

There was an in-depth discussion about the starting time for LMWH and the lack of evidence in this area. The committee discussed that there is a spectrum of opinion and practice around this, with initiation of LMWH ranging from 6-48 hours postoperatively. One of the studies included in this evidence review evaluated the initiation of LMWH from 6-8 hours postoperatively. The orthopaedic subgroup stated that this is not conventional practice. The committee considered that it was important to give surgeons flexibility to start prophylaxis depending on the complexity of the surgery and patient factors. The committee noted that the presence of postoperative bleeding complications are uncommon in spinal surgery, but emphasised that despite the low event rate when the complication does occur (such as bleeding in the spinal canal) it can be very serious. The committee considered that if the patient was going to develop a bleed this would usually be expected to occur within the first 24 hours post-surgery. Starting LMWH at 24 hours post-surgery was deemed acceptable, taking into consideration patient characteristics and bleeding risk. However due to the complex nature of orthopaedic spinal surgery, those being more cautious may wait longer than 24 hours (up to 48 hours) before initiating LMWH.

The committee and orthopaedic subgroup discussed that some surgeons may feel it is appropriate to start LMWH before 24 hours, for example if a patient has a history of VTE. It was stated that if LMWH is started before 24 hours post-operatively, it is essential that this is initiated only after an assessment by a senior clinician/consultant. This is to ensure that a low bleeding risk is accurately identified for the patient. The committee emphasised that this responsibility should not be given to junior clinicians. The committee acknowledged that the decision to commence LMWH earlier than 24 hours may be based on agreed local protocols for junior doctors to follow regarding when to seek multidisciplinary team and/or senior opinion.

The orthopaedic subgroup and committee noted that the following factors should be considered when deciding a time-point for post-operative initiation of LMWH: the risk of haemorrhage, amount of blood loss (high blood loss and the use of LMWH can distort the blood mechanism and increase bleeding) and risk of a VTE event.

The majority of spinal surgery is lumbar with no instrumentation (such as discectomies) which would be expected to take approximately 60 minutes. Discectomy patients are usually younger, generally fitter and mobilise within 24 hours and therefore very rarely require chemoprophylaxis. However it is important

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|---|---|
| | for clinicians to be aware that not every spinal surgery for disc prolapse is simple even in primary cases. Discectomies whether performed open or microscopically are at risk of haematoma formation.<br><br>More complex operations involving instrumentation can take much longer (4-5 hours). Duration of surgery is one of the three highly important risk factors for VTE listed by the committee, alongside immobilisation and surgical position. The committee noted that the duration of surgery cannot always be predicted, thus a patient's risk of developing VTE can change during the procedure. The second risk factor is post-surgical immobilisation which may be due to paralysis, deficit or pain. Most fixations allow for mobilisation, as most fixation is to stabilise the spine and mobilise the patient early. The third risk factor is the position of the patient during surgery. For lumbar surgeries, a majority of patients are placed in a prone position where the legs are lower level than the body (specifically the inferior vena cava), increasing the risk of thrombosis the longer the patient is in this position. |
| Trade-off between net clinical effects and costs | No relevant economic studies were identified for this population. Unit costs were presented to the committee.<br><br>The committee acknowledged the high risk of both VTE and bleeding in this population and the high cost of these events. The orthopaedic subgroup determined that based on the competing risks of these events, using mechanical prophylaxis would be the most clinically and economically justifiable option as the cost of mechanical prophylaxis provision would be off-set by the saving from the averted VTE events, while avoiding causing any increase in the risk of bleeding.<br><br>The committee acknowledged that in people with low risk of bleeding, the cost of adding pharmacological prophylaxis with LMWH (standard dose) would be justified given the high downstream costs of the VTE events that would be averted. However, the subgroup agreed that in absence of any economic evidence, the use of pharmacological prophylaxis should only be considered on individual basis based on proper risk assessment to ensure that the incremental cost of providing this extra prophylaxis is likely to be off-set in the longer term. |
| Other considerations | None. |

# 32 Cranial surgery

## 32.1 Introduction

Cranial surgery is usually completed by neurosurgeons and includes a range of operations including craniotomies for brain tumours and haemorrhages, including ruptured vascular lesions. The majority of these procedures are less than 6 hours duration but there are some that would last longer.

The various cranial surgical procedures can in some cases be associated with different risks of developing VTE and bleeding events. For example, people undergoing cranial surgery for brain tumours can be at increased risk developing VTE due to risk factors including leg paresis and the presence of hypercoagulable states. The risk of bleeding is of particular concern for patients requiring emergency cranial surgery.

It is crucial that clinicians weigh up the risk of VTE and risk of bleeding in this population, taking into account the surgical procedure itself.

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

For full details see review protocol in appendix C.

**Table 136: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) who are having intracranial surgery who are admitted to hospital, having day procedures or outpatients post-discharge |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological (no minimum duration):<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to |

| | |
|---|---|
| | maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists: warfarin (variable dose), acenocoumarol (all doses), phenindione (all doses)<br>• Fondaparinux (all doses)<br>• Apixaban (all doses)<br>• Dabigatran (all doses)<br>• Rivaroxaban (all doses)<br>• Aspirin (up to 300 mg) |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge<br>• Low versus high dose for LMWH only<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• Pulmonary embolism (symptomatic and asymptomatic) (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<br>• 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<br>• 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<br><br>Important outcomes:<br>• 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<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

| | |
|---|---|
| **Strata** | People who are contraindicated for pharmacological prophylaxis<br>People who are contraindicated for mechanical prophylaxis<br>People with intracranial tumour having neurosurgery |

## 32.3 Clinical evidence

Five studies were included in the review [49,76,115,199,312]; these are summarised in Table 137 below. Fourteen studies were included in the previous guideline (CG92) [2,43 49 76 115 199 211,234,271,295-297,312,313]. Six studies were excluded as they did not fit the population inclusion criteria for this review [2 234,271,295-297]. One study was excluded due to having an inappropriate comparison[43]. One paper was excluded as it did not report any relevant outcomes [313]. One paper was excluded as it was an abstract only[211]. One new study was included in the update[241] . Evidence from the included studies is summarised in the clinical evidence summary tables below (Table 138, Table 139, Table 140, Table 141, Table 142, Table 143). 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 137: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Cerrato 1978[49] | Intervention (n=50):<br>UFH 5000U, given 2 hours before surgery and 3x daily after for at least 7 days<br><br>Comparison (n=50):<br>No VTE prophylaxis | n=100<br><br>People having elective neurosurgery (meningiomas 31%, gliomas 29%, arterial aneurysms 13%. metastatic tumours 7% angiomas 5%, neurinomas 4% hemangioblastomas 3% craniopharyngiomas 2%, pituitary adenomas 1%, cavernous angiomas 1% arachnoid cysts 1%, chemodectomas 1%, epidurmoid tumours 1%)<br><br>Age: 40 years or over; mean intervention 53±9, control 51±7<br><br>Male to female ratio 1:1<br><br>Italy | DVT (8 days): 125I-labeled fibrinogen test | Strata: people with intracranial tumour having neurosurgery |
| Dickinson 1998 [76] | Intervention 1 (n=23):<br>LMWH, high dose (enoxaparin 30 mg pre-op, 30 mg 2x daily post-op), administered subcutaneously<br>+ sequential | n=66<br><br>People having neurosurgery for intracranial neoplasms | Mortality (30 days)<br><br>DVT (30 days): confirmed by duplex imaging (on four occasions in the first 1 month after surgery) | Strata: people with intracranial tumour having neurosurgery |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | compression device, thigh length<br><br>Intervention 2 (n=21):<br>LMWH, high dose (enoxaparin 30mg pre-op, 30 mg 2x daily post-op), administered subcutaneously<br><br>Intervention 3 (n=22):<br>Sequential compression device, thigh length | Age: range 50-100<br>Male and female<br><br>USA | PE (30 days): symptomatic<br><br>Major bleeding(30 days): intra-cerebral haemorrhage or epidural haematoma | |
| Goldhaber 2002[115] | Intervention (n=75):<br>LMWH, standard dose (enoxaparin 40 mg 1x daily)<br>+ IPCD<br><br>Comparison (n=75):<br>UFH 5000IU 2x daily<br>+ IPCD | n=150<br><br>People undergoing craniotomy with suspected or metastatic brain tumour<br><br>Age: mean intervention 48.33±15.07 years, comparison: 48.87±12.52 years<br><br>Male to female ratio 79:71<br><br>USA | Mortality (30 days)<br><br>DVT (30 days): confirmed by duplex ultrasonography<br><br>Major bleeding (30 days): major postoperative bleeding complications | Strata: people with intracranial tumour having neurosurgery |
| Macdonald 2003[199] | Intervention (n=51):<br>LMWH, low dose (Dalteparin 2500 IU 1x daily)<br><br>Comparison (n=49):<br>UFH 5000 IU 2x daily | n=100<br><br>People undergoing craniotomy for brain neoplasm, including trans-sphenoidal surgery, intracranial aneurysm, vascular malformation, infection, spontaneous intracranial hematoma, closed head injury or cortical resection for epilepsy<br><br>Diagnosis:<br>Brain tumour 63%<br>Aneurysm 15%<br>Microvascular decompression 6%<br>Chiari malformation 6% | Mortality (30 days)<br><br>DVT (7 days): confirmed by Doppler US<br><br>PE (30 days): symptomatic, confirmed by ventilation perfusion scan or spiral CT<br><br>Major bleeding (30 days): intracranial haemorrhage confirmed by CT scan and MRI<br><br>Thrombocytopaenia (30 days) | Strata: People having intracranial surgery (non-tumour) as tumour <80% |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | Vascular malformation 3%<br><br>Age: mean 51 ±15 years<br><br>Male to female ratio 23:28<br><br>USA | | |
| Wautrecht 1996[312] | Intervention (n=25): IPCD (thigh-length), from the night prior to the operation until at least 72 hours after the operation. AES, thigh-length pre-op continued for 10 days or until ambulant<br><br>Comparison (n=10): AES alone, from admission until discharge (hospital stay duration not reported) | n=35<br><br>People undergoing neurosurgery for brain tumours<br><br>No further details reported | DVT (8-10 days): confirmed by venography<br><br>PE (8-10 days): confirmed by pulmonary scintigraphy<br><br>Fatal PE (8-10 days): definition not reported | Strata: people with intracranial tumour having neurosurgery |

### 32.3.1 Strata: People undergoing intracranial surgery (non-tumour specific)

**Table 138: Clinical evidence summary: LMWH (low 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 Control | Risk difference with LMWH (low dose) versus UFH (95% CI) |
| All-cause mortality | 100 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.13 (0 to 6.55) | 20 per 1000 | 18 fewer per 1000 (from 20 fewer to 100 more) |
| DVT (symptomatic and asymptomatic) | 100 (1 study) 7 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.25 (0.45 to 117.6) | 0 per 1000 | Not estimable[e] |
| PE | 100 (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 40 fewer to 40 more)[c] |
| Fatal PE | 100 (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 40 fewer to 40 more)[c] |
| Major bleeding | 100 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.9 (0.19 to 18.67) | 20 per 1000 | 18 more per 1000 (from 16 fewer to 260 more) |
| Thrombocytopaenia | 100 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.9 (0.19 to 18.67) | 20 per 1000 | 18 more per 1000 (from 16 fewer to 260 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 Risk difference calculated in Review Manager
d Zero events in both arms
e Zero events in control arm

### 32.3.2 Strata: People with intracranial tumour having neurosurgery

**Table 139: 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 Control | Risk difference with UFH versus no VTE prophylaxis (95% CI) |
| DVT (symptomatic and asymptomatic) | 100 (1 study) 8 days | MODERATE[a] due to risk of bias | RR 0.18 (0.06 to 0.56) | 340 per 1000 | 279 fewer per 1000 (from 150 fewer to 320 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

**Table 140: Clinical evidence summary: LMWH (standard dose; standard duration) + IPCD versus UFH + IPCD**

| 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) + IPCD versus UFH + IPCD (95% CI) |
| All-cause mortality | 150 (1 study) 30 days | VERY LOW[c,d] due to risk of bias, imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000 (from 30 fewer to 30 more)[a] |
| DVT (symptomatic and asymptomatic) | 140 (1 study) 30 days | VERY LOW[c,d] due to risk of bias, imprecision | Peto OR 2.21 (0.73 to 6.65) | 67 per 1000 | 70 more per 1000 (from 17 fewer to 255 more |
| Major bleeding | 150 (1 study) 30 days | VERY LOW[c,d,e] due to risk of bias, indirectness, imprecision | Peto OR 1.97 (0.2 to 19.19) | 13 per 1000 | 13 more per 1000 (from 11 fewer to 193 more) |

a Risk difference calculated in Review Manager
b Zero events in both arms
c 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
d 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 Control | Risk difference with LMWH (standard) + IPCD versus UFH + IPCD (95% CI) |
| e Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes | | | | | |

**Table 141: Clinical evidence summary: LMWH (high dose; standard duration) +IPCD versus IPCD**

| 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)+IPCD versus IPCD (95% CI) |
| All-cause mortality | 45 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.96 (0.06 to 15.78) | 45 per 1000 | 2 fewer per 1000 (from 43 fewer to 384 more) |
| DVT (symptomatic and asymptomatic) | 45 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.28 (0.32 to 5.06) | 136 per 1000 | 38 more per 1000 (from 93 fewer to 554 more) |
| PE | 45 (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 80 fewer to 80 more)[c] |
| Fatal PE | 45 (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 80 fewer to 80 more)[c] |
| Major bleeding | 45 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.77 (0.77 to 78.78) | 0 per 1000 | Not estimable[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 confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Risk difference calculated in Review Manager
d Zero events in both arms
e Zero events in control arm

**Table 142: Clinical evidence summary: LMWH (high dose; standard duration) versus IPCD**

| 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 IPCD (95% CI) |
| All-cause mortality | 43 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.14 (0 to 7.15) | 45 per 1000 | 39 fewer per 1000 (from 45 fewer to 209 more) |
| DVT (symptomatic and asymptomatic) | 43 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.36 (0.05 to 2.74) | 136 per 1000 | 83 fewer per 1000 (from 129 fewer to 166 more) |
| PE | 43 (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 40 fewer to 40 more)[c] |
| Fatal PE | 43 (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 40 fewer to 40 more)[c] |
| Major bleeding | 43 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 8.15 (0.49 to 134.79) | 0 per 1000 | Not estimable[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 confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Risk difference calculated in Review Manager
d Zero events in both arms
e Zero events in control arm

**Table 143: 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 Control | Risk difference with IPCD + AES versus AES (95% CI) |
| DVT (symptomatic and | 23 | VERY LOW[a,b] | Peto OR 0.01 | 400 per 1000 | 393 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 IPCD + AES versus AES (95% CI) |
| asymptomatic) | (1 study)<br>8-10 days | due to risk of bias, imprecision | (0 to 0.25) | | (from 257 fewer to 400 fewer) |
| PE | 35<br>(1 study)<br>8-10 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 130 fewer to 130 more)[c] |
| Fatal PE | 35<br>(1 study)<br>8-10 days | VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 130 fewer to 130 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 Risk difference calculated in Review Manager
d Zero events in both arms
e Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

## 32.4 Economic evidence

No relevant health economic studies were identified.

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

## 32.5 Evidence statements

**Clinical**

*People undergoing intracranial surgery (non-tumour surgery)*

LMWH at a low dose for a standard duration was compared with UFH, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, fatal PE, major bleeding and heparin-induced thrombocytopaenia were reported in one study. There was possible clinical benefit of LMWH in terms of all-cause mortality, however the result may also have been consistent with no difference. There was possible clinical harm in terms of DVT (symptomatic and asymptomatic), major bleeding and heparin-induced thrombocytopaenia, however the large uncertainty around these results was also consistent with no difference or benefit. There was no clinical difference in terms of PE and fatal PE, although again there was large uncertainty around these results. The quality of the evidence was very low due to risk of bias and imprecision.

*People with intracranial tumour having neurosurgery*

UFH was compared with no prophylaxis, the outcome DVT (symptomatic and asymptomatic) was reported in one study. There was clinical benefit of UFH in terms of DVT (symptomatic and asymptomatic). The quality of the evidence was moderate due to risk of bias.

LMWH at a standard dose for a standard duration in combination with IPCD was compared with UFH in combination with IPCD, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic) and major bleeding were reported in one study. There was possible clinical harm of LMWH in combination with IPCD in terms of DVT and major bleeding, although there was uncertainty around these results. There was no clinical difference in terms of all-cause mortality. The quality of the evidence was very low due to risk of bias, imprecision and indirectness.

LMWH at a high dose for a standard duration in combination with IPCD was compared with IPCD, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, fatal PE and major bleeding were reported in one study. There was possible clinical benefit of LMWH in combination with IPCD in terms of all-cause mortality and DVT (symptomatic and asymptomatic). There was possible clinical harm of LMWH in terms of major bleeding and there was no clinical difference in terms of PE and fatal PE. All these results were associated with large confidence intervals and therefore are considerably uncertain. The quality of the evidence was very low due to risk of bias and imprecision.

LMWH at a high dose for a standard duration was compared with IPCD, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, fatal PE and major bleeding were reported in one study. There was possible clinical benefit of LMWH in combination with IPCD in terms of all-cause mortality and DVT (symptomatic and asymptomatic). There was possible clinical harm of LMWH in terms of major bleeding and there was no clinical difference in terms of PE and fatal PE. All these results were associated with large confidence intervals and therefore are considerably uncertain. The quality of the evidence was very low due to risk of bias and imprecision.

IPCD in combination with AES was compared with AES alone, the outcomes DVT (symptomatic and asymptomatic), PE and fatal PE. There was clinical benefit of IPCD in terms of DVT (symptomatic and

asymptomatic), and no clinical difference in terms of PE and fatal PE, although the PE outcomes were very uncertain. The quality of the evidence was very low due to risk of bias, indirectness and imprecision.

**Economic**

- No relevant economic evaluations were identified.

## 32.6 Recommendations and link to evidence

| | |
|---|---|
| **Recommendations** | **1.5.24 Consider mechanical VTE prophylaxis for people undergoing cranial surgery. [2018]**<br><br>**1.5.25 If using mechanical VTE prophylaxis for people undergoing cranial surgery, start it on admission. Choose either:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression.**<br><br>**Continue for 30 days or until the person is mobile or discharged, whichever is sooner. [2018]**<br><br>**1.5.26 Consider adding pre-operative pharmacological VTE prophylaxis with LMWH[w]. 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]**<br><br>**1.5.27 Consider adding pharmacological VTE prophylaxis with LMWH[x] , 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]**<br><br>**1.5.28 If needed, start LMWH[y] 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]**<br><br>**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]** |

[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), 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.

[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.

| 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.<br><br>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 thrombocytopaenia (duration of study) and technical complications of mechanical interventions (duration of study) as important outcomes.<br><br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Five randomised controlled trials were included in this review. All of the studies were included in the previous guideline (CG92). The committee pre-specified a stratum of people with intracranial tumour having neurosurgery; four studies were included in this stratum and one study was non-tumour specific (a combined population covering all intracranial surgery). A total of six intervention comparisons were identified from the five studies included, with one of the studies being a three-arm trial. These comparisons evaluated the use of pharmacological (different doses of LMWH and UFH) and mechanical prophylaxis (IPCD and AES) in people undergoing intracranial surgery.<br><br>The one study in a non-tumour specific intracranial population evaluated the use of LMWH (low prophylactic dose) versus UFH. This study reported data for all of the critical outcomes and heparin-induced thrombocytopaenia. All of the evidence in this comparison was graded very low due to risk of bias and imprecision.<br><br>The committee noted that where available, most of the evidence came from small studies likely to be underpowered. Therefore they were not surprised that much of the evidence was of lower quality due to imprecision. |
| Trade-off between clinical benefits and harms | It was suggested that this section encompass all cranial surgery on the understanding that this involves procedures carried out by a neurosurgeon. This was chosen as a more generic term than intracranial surgery as some operations to remove tumours do not necessarily involve opening the dura. For example, if a tumour is at the base of the skull it will still be dealt with by a neurosurgeon. There may be multidisciplinary involvement with oral and ENT surgeons but this will usually be for assistance with access, with the condition itself still sitting within neurosurgery. The committee acknowledge that this definition encompasses minor cranial surgeries (bony lumps) as well as other relatively minor operations undertaken by neurosurgeons on nerves in the arms and legs (peripheral nerve surgery) such as carpal tunnel decompression. However, the committee reiterate that the guideline cannot pragmatically cover every different surgery separately and that these patients will likely be assessed as low or very low risk for VTE at the risk assessment stage due to their usually having short (<60-90 mins) day case surgeries.<br><br>There are different levels of VTE risk associated with neurosurgery to remove intracranial tumours based on the type of tumour. Surgery for benign tumours (meningioma's and acoustic tumours) tends to last longer (3-8+ hours) than surgery for malignant tumours (primarily gliomas and metastases) which usually involves biopsy which may take 1.5-2 hours or open operation of ~4 hours. However those people undergoing cranial surgery for malignant tumours will usually be assessed as at increased risk of VTE due to the 'active cancer' risk factor. Given that all people |

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| | undergoing cranial surgery would have at first been assessed for risk of VTE based on these factors, the committee did not deem it necessary to write separate prophylaxis recommendations based on the tumour type.<br><br>The committee discussed the evidence alongside the previous recommendation made in CG92. In CG92 this population was merged with recommendations for people undergoing spinal surgery (jointly termed neurological surgery). While the evidence in the more specific cranial surgery population included in this update was mostly of very low quality due largely to imprecision around the effect estimates, the committee considered the evidence generally supported the recommendations made in the previous guideline – use of mechanical prophylaxis as first option with the addition of pharmacological prophylaxis for those at increased risk of VTE above their risk of bleeding. However the committee considered that a softer 'consider' recommendation was more appropriate for this population to reflect the uncertainty of the evidence.<br><br>The committee also discussed the duration of prophylaxis. For mechanical it was discussed that once mobile, mechanical prophylaxis would not be necessary and therefore prophylaxis should be stopped. However, they also noted that some patients may be immobile for a long time and require rehabilitation in a non-acute setting. As there is no evidence for extended prophylaxis the committee added an upper limit of 30 days mechanical prophylaxis for this patient group in line with the recommendation for stroke patients. Pharmacological prophylaxis is recommended for a minimum of 7 days as with the recommendations for other populations. |
| Trade-off between net clinical effects and costs | No economic studies have been included in this review. Relevant unit costs were presented. The committee acknowledged that this is a population at high risk of bleeding, and hence mechanical prophylaxis options (for example IPCD) would be preferable in terms of safety and avoidance of major bleeding. For those at low risk of bleeding, LMWHs (standard dose) were considered to have the most favourable benefit-harm balance. This was supported by their slightly lower total drug and monitoring costs compared to UFH, making them the likely cost effective option among the pharmacological prophylaxis options considered. |
| Other considerations | Clinical practice has changed within this population since the last guideline was published. Less invasive surgeries are being used and more clinicians are encouraging earlier mobilisation and hydration. Whilst these factors reduce VTE risk, not all patients mobilise soon after surgery and co-morbidities remain common in this population.<br><br>The recommendation against pharmacological prophylaxis for people with haemorrhage is also expected to encompass people with traumatic brain injury or head injury. This recommendation is also cross-referred to from the major trauma section. While people with head injury may have suspected haemorrhage and the wording of the recommendation suggests that the haemorrhage has already been identified, the committee suggested that once a person has been admitted following trauma, standard practice is to have a scan to identify or exclude the presence of haemorrhage, and therefore it was acceptable to cross-refer to the recommendation in this cranial surgery population.<br><br>The committee decided to make a cautionary recommendation for people fitted with intracranial devices as it is believed that people fitted with the two most common devices listed in the recommendation may be at increased risk of bleeding. |

# 33 Spinal injury

## 33.1 Introduction

Spinal injury and, in particular, spinal cord injury is a significant cause of morbidity and mortality with younger age groups frequently affected. Spinal injury can occur with or without injury to the spinal cord or cauda equina. Even without injury to the spinal cord or cauda equina, patients with spinal injury may be at increased risk of VTE for reasons of prolonged immobility.

Non-traumatic causes of spinal cord compression are covered in other guidelines, for example in the NICE Metastatic spinal cord compression guideline CG75[225]. However, further evidence is evaluated in the palliative care (chapter 19) and critical care (chapter 20) sections of this guideline. The evidence for patients undergoing elective spinal surgery is presented in chapter 31.

The major concern in this population is the constantly changing balance between the initial risk of bleeding (potentially a catastrophic complication within the enclosed space of the spine) and the subsequent increased risk of thrombotic events, particularly with prolonged immobilisation.

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

For full details see review protocol in appendix C.

**Table 144: PICO characteristics of review question**

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|---|---|
| **Population** | Adults and young people (16 years and older) with cord or spinal column injury who are:<br>• Admitted to hospital<br>• Outpatients post-discharge |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*)<br>○ 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*)<br>○ tinzaparin (standard prophylactic dose 3500-4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) |

| | |
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| | ○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300 mg)*<br><br>*off-label |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• Pulmonary embolism (symptomatic and asymptomatic) (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<br>• 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 returning to theatre for surgery for control of bleeding and epidural bleeding<br>• 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<br><br>Important outcomes:<br>• 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 |

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| | attention and/or a change in antithrombotic therapy.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

## 33.3 Clinical evidence

Four studies were included in the review[122,212,276]; these are summarised in Table 145 below. Four studies were included in the previous guideline (CG92) [122,123,212,276], one of which was excluded due to having an inappropriate conjunct to the intervention[123]. One new study[127] was identified during the update. Evidence from these studies is summarised in the clinical evidence summary below (Table 146, Table 147, Table 148, Table 149). 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 145: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Green 1990[122] | Intervention (n=20):<br>LMWH - standard dose (tinzaparin 3500U 1x daily), administered subcutaneously<br><br>Comparison (n=21):<br>UFH 5000U 3x daily, administered subcutaneously | n=41<br><br>People with complete motor paralysis after spinal cord injury, sustained with previous 72 hours<br><br>Age: intervention mean 28.3±11.8; comparison 31.4±15.5<br><br>Male to female ratio 34:7<br><br>USA | All-cause mortality (56 days)<br><br>Fatal PE (56 days). Confirmed by: autopsy<br><br>DVT (56 days). Screened with impedance plethysomography, Doppler flow measurement and DUS, 2 patients confirmed by venography, 1 patient confirmed by symptom and abnormal flow study<br><br>Major bleeding (56 days): reported fatal bleeding only | |
| Halim 2014[127] | Intervention (n=37):<br>LMWH, standard dose (enoxaparin 40mg 1x daily), started on day of admission and continued for 8 weeks<br><br>Comparison (n=37):<br>no pharmacological VTE prophylaxis<br><br>Both groups received concomitant | n=74<br><br>People with acute spinal cord injury (≤5 days)<br><br>Age not reported<br><br>Male to female ratio 60:14<br><br>Ethnicity: Indian<br><br>India | DVT (12-16 days): colour Doppler venous ultrasonography<br><br>PE (12-16 days): symptomatic, identified by clinical assessment | |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | mechanical prophylaxis such as AES | | | |
| Merli 1988[212] | Intervention (n=19): UFH 5000U 3x daily, administered subcutaneously<br><br>Comparison (n=17): placebo | n=53<br><br>People with acute spinal cord injury (classified as having either motor complete or incomplete-preserved motor, non-functional C2 to T11 lesions), injured <2 weeks before initial evaluation<br><br>Age: >16 years old<br>Gender not reported<br><br>USA | DVT (28-42 days). Diagnosed by fibrinogen uptake test confirmed by venography. | Treatment reduced from 42 to 28 days once it was found that patients were being discharged earlier. Unclear how many received 42 days treatment. |
| Spinal Cord Injury Thromboprophylaxis Investigators 2003 [276] | Intervention (n=230): LMWH – high dose (Enoxaparin 30mg 2x daily), administered subcutaneously<br><br>Comparison (n=246): UFH 5000U 3x daily, administered + IPCD used at least 22 hours/day<br><br>Start time: within 72 hours of injury<br>Duration: 2 weeks | n=476<br><br>People with acute spinal cord injury (from spinal cord level C2 to T12), sustained within previous 72 hours<br><br>Age: mean 36.9 years<br><br>Male to female ratio 389/87<br><br>USA, Canada | All-cause mortality (56 days)<br><br>Fatal PE (56 days). Confirmed by: ventilation-perfusion lung scan, spiral CT or pulmonary angiography at 2 weeks or 2 days after last dose<br><br>PE (56 days). Confirmed by: ventilation-perfusion lung scan, spiral CT or pulmonary angiography at 2 weeks or 2 days after last dose<br><br>DVT (56 days). Confirmed by: proximal and distal venography or proximal Doppler Ultrasound 2 weeks or 2 days after last dose<br><br>Major bleeding (56 days): definition not reported | Over 3/4 of patients randomised were excluded from efficacy analysis because they either failed to receive adequate proximal and distal imaging, or discontinued study due to bleeding or platelet counts <100 x $10^9$/L |

**Table 146: Clinical evidence summary: UFH 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 placebo | Risk difference with UFH (95% CI) |
| DVT | 33<br>(1 study) | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 1.06<br>(0.53 to 2.15) | 471 per 1000 | 28 more per 1000<br>(from 221 fewer to 541 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 147: 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) |
| DVT | 74<br>(1 study)<br>12-16 days | MODERATE[a]<br>due to imprecision | RR 0.25<br>(0.06 to 1.1) | 216 per 1000 | 162 fewer per 1000<br>(from 203 fewer to 22 more) |
| PE | 74<br>(1 study)<br>12-16 days | VERY LOW[a,d,e]<br>due to risk of bias, indirectness, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 50 fewer to 50 more)[b] |
| Fatal PE | 74<br>(1 study)<br>12-16 days | VERY LOW[a,d,e]<br>due to risk of bias, indirectness, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 50 fewer to 50 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 Risk difference calculated in Review Manager
c Zero events in both arms

| 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) |
| d 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<br>e Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes | | | | | |

**Table 148: 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 (standard dose) (95% CI) |
| All-cause mortality | 41<br>(1 study)<br>56 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.14<br>(0.01 to 2.24) | 95 per 1000 | 81 fewer per 1000<br>(from 94 fewer to 96 more) |
| Fatal PE | 41<br>(1 study)<br>56 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.14<br>(0.01 to 2.24) | 95 per 1000 | 81 fewer per 1000<br>(from 94 fewer to 96 more) |
| DVT | 41<br>(1 study)<br>56 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.13<br>(0.01 to 1.31) | 143 per 1000 | 122 fewer per 1000<br>(from 141 fewer to 36 more) |
| Major bleeding | 41<br>(1 study)<br>56 days | VERY LOW[a,b,e]<br>due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 90 fewer to 90 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<br>b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs<br>c Risk difference calculated in Review Manager<br>d Zero events in both arms<br>e Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes | | | | | |

**Table 149: Clinical evidence summary: LMWH (high dose; standard duration) versus UFH+ICPD**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with UFH+IPCD | Risk difference with LMWH (standard dose) (95% CI) |
| All-cause mortality | 476 (1 study) 56 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.07 (0.15 to 7.53) | 8 per 1000 | 1 more per 1000 (from 7 fewer to 53 more) |
| Fatal PE | 107 (1 study) 56 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 40 fewer to 40 more)[c] |
| PE | 107 (1 study) 56 days | LOW[a,b] due to risk of bias, imprecision | RR 0.28 (0.08 to 0.98) | 184 per 1000 | 132 fewer per 1000 (from 4 fewer to 169 fewer) |
| DVT | 107 (1 study) 56 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.34 (0.92 to 1.95) | 449 per 1000 | 153 more per 1000 (from 36 fewer to 427 more) |
| Major bleeding | 476 (1 study) 56 days | VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision | RR 0.49 (0.19 to 1.28) | 53 per 1000 | 27 fewer per 1000 (from 43 fewer to 15 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 Risk difference calculated in Review Manager
d Zero events in both arms
e Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

## 33.4 Economic evidence

**Published literature**

No relevant health economic studies were identified.

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

## 33.5 Evidence statements

**Clinical**

UFH was compared with no prophylaxis, the outcome DVT (symptomatic and asymptomatic) was reported in one study. There was no clinical difference in terms of this outcome; although the inconsistency associated with the result means the outcome may also mean either a benefit or harm. The quality of the evidence was very low due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration was compared with no prophylaxis, DVT (symptomatic and asymptomatic), PE and fatal PE was reported in one study. There was possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic), however the uncertainty means that this result may also be consistent with no difference. There was no clinical difference in terms of PE and fatal PE. However these results were also very uncertain. The quality of the evidence ranged from very low to moderate due to risk of bias, indirectness and imprecision.

LMWH at a standard dose for a standard duration was compared with UFH, all-cause mortality, DVT, fatal PE and major bleeding were reported in one study. There was possible clinical benefit of LMWH in terms of all-cause mortality, DVT (symptomatic and asymptomatic), fatal PE. There was no clinical difference in terms of major bleeding. However all results were very uncertain and could be consistent with harm, no difference, or benefit. The quality of the evidence was very low due to risk of bias, imprecision and indirectness

LMWH at a high dose for a standard duration was compared with UFH in combination with IPCD, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, fatal PE and major bleeding. There was possible clinical benefit of LMWH in terms of PE and major bleeding. There was possible clinical harm of LMWH in terms of all-cause mortality and DVT (symptomatic and asymptomatic). Although uncertainty means these results may also have been consistent with no difference. The quality of the evidence ranged from very low to low due to risk of bias, imprecision and indirectness.

**Economic**

No relevant economic evaluations were identified.

## 33.6 Recommendations and link to evidence

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|---|---|
| **Recommendations** | **1.5.30 Consider mechanical VTE prophylaxis on admission for people with spinal injury. Choose either:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression. [2018]**<br><br>**1.5.31 Reassess risk of bleeding 24 hours after initial admission in people with spinal injury. [2018]** |

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| | **1.5.32 Consider adding pharmacological VTE prophylaxis with LMWH[z] 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]**<br><br>**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]** |
| **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 thrombocytopaenia and technical complications of mechanical interventions to be important outcomes.<br>Please see section 4.4.3 in the methods chapter for further detail explaining prioritisation of the critical outcomes. |
| Quality of the clinical evidence | The majority of evidence was of very low quality with a high risk of bias. All of the evidence had imprecision. Some of the evidence was downgraded for indirectness as the definition of the outcome of the study or the time point at which the outcome was measured did not match the protocol or was not reported.<br>The committee noted that the majority of studies had low numbers of participants or with high missing data rates, in particular the largest study (n=476) where no endpoint data was collected for 75% of patients due to inadequate imaging to determine endpoint or discontinued the study due to bleeding or platelet counts <100 x 109/L. |
| Trade-off between clinical benefits and harms | People with spinal injury can be paraplegic or immobile for a period of time and so are at high risk of VTE. The committee considered that the greatest risk period is more than 3 days and up to a week. However most spinal patients are immobile for 3 months. The committee noted that some people will have comorbid brain injury. All people with spinal injuries will also have a degree of haematoma, and people with spinal fracture may have significant haematoma.<br>Very little evidence was identified for forms of mechanical prophylaxis, with only one paper reporting use of IPCD in combination with UFH, and no evidence for the use of AES. The committee noted that there is a higher risk of technical complications of mechanical interventions in this population (for example bruising) due to lower mobility, which was not identified in the studies. The committee was of the view that there is a lot of confusion and variation in current practice in this area; that AES and IPCD are used initially and then, if there are no plans to operate, pharmacological prophylaxis is considered later on. The committee highlighted that bleeding in this population would have catastrophic consequences and therefore pharmacological prophylaxis has to be avoided in the early stages after admission. Due to the sensory neurological impairment in the legs and that fact that much of this population will be at increased risk of VTE due to immobilisation, the committee agreed that mechanical prophylaxis should be considered on admission, but that due to the increased chances of complications such as skin damage, it is extremely important that AES are fitted correctly.<br>The committee agreed that if there are no plans to operate, anticoagulation at prophylactic doses can start 24 hours after the spinal injury where there is a low |

[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.

| | |
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| | bleeding risk (from the brain). The committee noted that as a clot takes roughly 2 hours to stabilise, the time frame of 24 hours for initiating anticoagulation at prophylactic doses was considered to be feasible and clinically sensible.<br>The committee also discussed when prophylaxis should be stopped. They agreed that for paraplegic patients, pharmacological prophylaxis should be stopped when the patient is out of the immediate risk period. This is at the individual discretion of the clinician and would take account of the presence of bed/joint mobilisation exercises. The committee noted that for people with spinal cord injury, there is a chance that pre-morbid mobility may not be regained. In some cases prophylaxis may continue during rehabilitation under specialist supervision. However, it was decided to recommend prophylaxis is only continued for 30 days or until the person is mobile or discharged, whichever is sooner. The 30 days is extrapolated from evidence from the stroke population evidence related to the duration of IPC prophylaxis. The committee acknowledge that this may be an arbitrary cut off but wanted to ensure patients do not get prophylaxis for a long period for which there is no evidence to support. Clinicians can reassess a patient's need for prophylaxis if their risk goes on beyond 30 days. |
| Trade-off between net clinical effects and costs | No economic studies have been included in this review. Relevant unit costs were presented. The committee acknowledged that this is a population at high risk of VTE due to long periods of immobilisation. The committee considered that the cost of prophylaxis is likely to be off-set by the avoidance of the costly VTE events. However, the committee highlighted that this population is also at high risk bleeding, particularly in the immediate 24-hour period following the injury. Hence, mechanical prophylaxis options would be preferable in terms of safety and avoidance of major bleeding during the early period after the event.<br>Given the rapidly changing VTE and bleeding risk balance in this population; reassessment of these risks was considered essential for guiding the appropriate prescribing of prophylaxis, and hence maximising its value. The committee acknowledged that reassessment will involve extra use of resources in terms of staff time, however this was considered to be justified as this cost will be off-set by the avoidance of the costly VTE and bleeding events that could result from under- or over-use of prophylaxis.<br>Once bleeding risk is low enough, pharmacological prophylaxis could be prescribed. The committee agreed that, based on the clinical evidence, LMWHs (standard dose) were considered more effective compared to UFH. They also had slightly lower total drug and monitoring costs compared to UFH, making them the likely cost effective option among the pharmacological prophylaxis options considered. |
| Other considerations | None. |

# 34 Major trauma

## 34.1 Introduction

The majority of patients suffering major trauma require assessment and management by the orthopaedic trauma service. There may be associated injury to the head, chest or abdomen in those patients sustaining poly-trauma, most frequently occurring following road traffic collisions. However, major pelvic and spinal injuries and multiple long bone fractures in isolation constitute significant orthopaedic trauma. A proportion will require management in a critical care setting, in either an intensive care or high dependency unit, for which additional guidance can be found in Chapter 20 of this guideline.

For major trauma patients, the main concern is the constantly changing balance between the initial risk of bleeding and the subsequent increased risk of thrombotic events. Trauma patients have been identified to be at increased risk of VTE.

More guidance related to VTE prophylaxis for patients with single injury musculoskeletal trauma can be found in the chapters on lower limb immobilisation (chapter 24), fragility fractures of the pelvis, hip and proximal femur (chapter 25), foot and ankle surgery (chapter 29) and spinal injury (chapter 33) in this guideline.

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

For full details see review protocol in appendix C.

**Table 150: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) who are attending hospital with major trauma |
| **Interventions** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br>• Vena caval filters<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>  ○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*)<br>  ○ 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*)<br>  ○ tinzaparin (standard prophylactic dose 3500-4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*)<br>• LMWH, licensed in countries other than UK: |

| | |
|---|---|
| | ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300 mg)*<br>*off-label |
| **Comparisons** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis.<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

## 34.3 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of mechanical and pharmacological prophylaxis strategies (alone or in combination) in people with major trauma. Of the five studies included in the previous guideline conducted in the major trauma population (CG92), four studies were included[112,113,166,278], and one study was excluded.[60] Six new studies were also included.[9,74,82,103,165,173] Additionally the committee decided that vena caval filters would only be appropriate for consideration for VTE prophylaxis in the major trauma population, therefore the studies included in the previous guideline on the effectiveness of vena caval filters were considered here. There was one study[73] noted for consideration in CG92, however this was excluded in this guideline as it looked at the effectiveness of vena caval filters for secondary prevention of VTE. The included studies are summarised in Table 151 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.

**Table 151: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Anglen 1998[9] | Intervention (n=68):<br>IPCD, below knee<br><br>Comparison (n=49):<br>foot pump, applied to both feet (intermittent plantar compression devices, Plexipulse foot pumps)<br><br>Applied after surgery or in the case of significant preoperative delay, before surgery | n=117<br><br>People with trauma (pelvis 10.3%, hip 6.8% , acetabulum 32.5%, femur 43.6%, combination 6.8% fracture, multi trauma 61.5%)<br>ISS not reported<br><br>Age >17 years<br>Males and females (65:52)<br><br>United States | DVT (up to 14 days): confirmed by duplex ultrasound<br><br>PE (2 months): method of confirmation not reported | Major trauma status not defined as no ISS data reported. |
| Dennis 1993[74] | Intervention 1 (n=189):<br>IPCD, full leg<br>Device applied within 48 hours of injury, until discharge or fully ambulatory<br><br>Intervention 2 (n=92): | n=395<br><br>People with trauma (chest 29.9%, abdomen 23.3%, extremities 47.6%, head 23.3%, spinal cord 12.7%, paralysis | All-cause mortality (time-point not reported)<br><br>DVT (time-point not reported): confirmed by duplex scanning or Doppler ultrasound | Trauma inclusion defined as ISS >9<br><br>Patients had scanning at 48 hrs and then |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | UFH (5000U 2 x daily)<br>Started within 96 hours of injury, until discharge or fully ambulatory<br><br><u>Comparison (n=114):</u><br>no VTE prophylaxis | 6.3%)<br>ISS >9<br><br>Age >18 years<br>Gender not reported<br><br>United States | PE (time-point not reported): confirmed by duplex scanning or Doppler ultrasound<br><br>Fatal PE (time-point not reported): confirmed by autopsy | every 5 days after injury for between 2-25 scans |
| Elliot 1999[82] | <u>Intervention (n=74):</u><br>IPCD, full leg<br>Duration not reported<br><br><u>Comparison (n=75):</u><br>foot pump (plantar venous intermittent pneumatic compression devices)<br>Duration not reported | n = 149<br><br>People with major trauma (head 82.6%, face 24.8%, chest 55.7%, abdomen 26.2%, upper limb 13.4%, other 38.9%)<br>ISS: intervention mean, SD = 31, 11.6; comparison mean, SD = 30.2, 13.1<br><br>Age >13 years<br>Males and females (100:49)<br><br>United States | All-cause mortality (time-point not reported)<br><br>DVT (8 days): confirmed by compression duplex ultrasonography<br><br>Major bleeding (time-point not reported): definition not reported | |
| Fuchs 2005[103] | <u>Intervention (n=111):</u><br>• Continual passive motion, 2 x daily<br>• UFH 5000U 3 x daily<br><br><u>Comparison (n=116):</u><br>UFH 5000U 3 x daily<br><br>Treatment started on the evening before surgery or immediately following surgery in emergency cases, carried on until mobilisation | n = 227<br><br>People with bony or ligamentous trauma to the spine, pelvis, femur, tibia or ankle<br>ISS not reported<br><br>Age >18 years<br>Males and females (131:96)<br><br>Germany | All-cause mortality (3 months)<br><br>DVT (3 months): confirmed by compression ultrasonography, Doppler and/or plethysmography, and venography<br><br>PE (3 months): method of confirmation not reported | Major trauma status not defined as no ISS data reported. |
| Geerts 1996[112] | <u>Intervention (n=136):</u><br>UFH 5000U, given subcutaneously every 12 hours<br>Duration: within 36 hours of the injury for up to 14 days. | n=265<br><br>People with major trauma (head 4.9%, face/chest/abdomen 37.7%, spine 15%, lower limb 54.3%)* | All-cause mortality (14 days)<br><br>DVT (days 10-14):confirmed by venography | Trauma inclusion defined as ISS >9 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison (n=129): LMWH, high dose (enoxaparin), 30 mg, given subcutaneously every 12 hours<br>Duration: within 36 hours of the injury for up to 14 days. | ISS >9<br><br>Age (mean, SD): intervention group 37.0 (16.5), comparison group 39.1 (16.8)<br><br>Males and females (192:73)<br><br>Canada<br><br>*some patients had injuries at more than one site | PE, symptomatic (14 days): confirmed by ventilation perfusion scan<br><br>Major bleeding (14 days): defined as overt bleeding that was associated with a decrease in the haemoglobin level of at least 2g per decilitre, the transfusion of two or more units of packed red cells, an intracranial or retroperitoneal site of bleeding, or the need for surgical intervention<br><br>Fatal PE (14 days): confirmed by autopsy | |
| Ginzburg 2003[113] | Intervention (n=224): IPCD, below knee<br>Duration: within 24hrs of trauma until walking independently or discharge from hospital. Maximum 8 consecutive hours disuse allowed<br><br>Comparison (n=218): LMWH, high dose (enoxaparin), 30 mg, given subcutaneously every 12 hours<br>Duration: within 24 hours of the injury until walking independently or discharge from hospital | n=442<br><br>People with high risk trauma (head 22.9%, spinal cord 7.5%, chest 37.3%, leg or pelvis fracture 35.1%)*<br>ISS >9<br><br>Age (mean): intervention group 40, comparison group 42)<br><br>Males and females (327:115)<br><br>United states<br><br>*some patients had injuries at more than one site | All-cause mortality (30 days)<br><br>DVT (30 days): confirmed by Doppler ultrasonography<br><br>PE, symptomatic (30 days): confirmed by spiral computed tomography or ventilation-perfusion scintigraphy<br><br>Major bleeding (30 days): defined as haemorrhage leading to a fall in haemoglobin conc. of 2 g/dl, transfusion of 2 or more of packed red blood cells, intracranial or retroperitoneal bleeding or bleeding requiring surgical intervention | Includes moderately (ISS 9-19) and severely (ISS >19) injured people. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Knudson 1994[165] | Group 1 (patients who could receive either methods of prophylaxis):<br>Intervention 1 (n=44):<br>UFH (5000U, 2 x daily)<br><br>Intervention 2 (n=32):<br>• IPCD, full leg<br>• AES, undefined<br><br>Comparison (n=64):<br>No VTE prophylaxis<br><br>Duration not reported | n=251<br><br>People with trauma (laparotomy, thoracotomy, ventilated > 24 hours, spine, pelvic, femur fracture)<br>Mean ISS 16 (range 10-66)<br><br>Age > 18 years<br>Males and females (200:51)<br><br>United States | All-cause mortality<br><br>DVT (3 weeks): confirmed by duplex imaging<br><br>PE (3 weeks): confirmed by pulmonary angiography | Cause of major trauma unclear for all patients<br><br>Unclear if patients in group 3 received AES |
| | Group 2 (patients who could not wear mechanical prophylaxis devices):<br><br>Intervention (n=19):<br>UFH (5000U, 2 x daily)<br><br>Comparison (n=27):<br>No VTE prophylaxis<br><br>Duration not reported | | | |
| | Group 3 (patients who had contraindication to heparin):<br>Intervention (n=26):<br>IPCD, full leg<br><br>Comparison (n=39):<br>No VTE prophylaxis<br>Duration not reported | | | |
| Knudson 1996[166] | Intervention (n=120):<br>LMWH, high dose (enoxaparin) 30mg given subcutaneously every 12 hours<br>Duration not reported<br><br>Comparison (n=82):<br>• IPCD, length undefined<br>• AES, length undefined<br>Or FID alone | n=202<br><br>People with trauma injuries (venous injury, pelvic fracture, unstable spine, spinal fracture)<br>ISS > 10<br><br>Age (mean): 38.5 years<br>Male and female (values not reported) | All-cause mortality (time-point not reported)<br><br>DVT (time-point not reported): confirmed by venous duplex ultrasound<br><br>PE (time-point not reported): method of confirmation not reported<br><br>Fatal PE (time-point not reported): confirmed by | Trauma inclusion defined as ISS >10<br><br>Different mechanical prophylaxis used depending on the condition of the lower extremity. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Sequential gradient pneumatic compression sleeves worn over AES, or arteriovenous impulse device<br>Duration not reported | United States | autopsy | |
| Kurtoglu 2004[173] | Intervention (n = 60):<br>• LMWH, standard dose (enoxaparin) 40mg given once daily<br>• IPCD, below knee<br><br>Comparison (n = 60):<br>IPCD, below knee<br><br>All patients received IPCD on admission, and initiation of LMWH was determined after CT within 24 hours of admission. Duration not reported | n = 120<br><br>People with severe head/spinal trauma (head 90.1%, spinal 9.1%)<br>ISS 4-35<br><br>Age >14 years<br>Male and female: 47:73<br><br>Turkey | All-cause mortality (time-point not reported)<br><br>DVT (time-point not reported): confirmed by duplex sonography<br><br>PE (time-point not reported): confirmed by spiral CT<br><br>Major bleeding (time-point not reported): defined as macroscopic haematuria without renal injury, overt bleeding, and a sudden drop in haemoglobin level (>2 g/dl)<br><br>Fatal PE (time-point not reported): confirmed by spiral CT | No definition of 'severe' trauma provided. |
| Stannard 2006[278] | Intervention (n=97):<br>LMWH, high dose (enoxaparin), 30mg, given subcutaneously every 12 hours<br>Duration: within 24-48 hours of the injury<br><br>Comparison (n=103):<br>Pulsatile foot pumps at time of admission (patients asked to use it for at least 12 hours per day) combined with enoxaparin (high dose, 30mg every 12 hours) on a delayed basis (5 days after admission) | n=200<br><br>People with recent blunt skeletal trauma (mean ISS 14.42, range 4-57)<br><br>Age >18 years<br><br>United States | All-cause mortality (time point not reported)<br><br>DVT (24 hours before discharge): confirmed by bilateral magnetic resonance venography and ultrasonography<br><br>PE, symptomatic (time point and method of confirmation not reported)<br><br>Fatal PE (time point and method of confirmation not reported) | Blunt trauma |

**Table 152: Clinical evidence summary: IPCD (full leg) versus no 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 IPCD (full leg) versus no prophylaxis (95% CI) |
| All-cause mortality | 368 (2 studies) 7-90 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.3 (0.06 to 1.62) | 26 per 1000 | 18 fewer per 1000 (from 25 fewer to 16 more) |
| DVT (symptomatic and asymptomatic) | 368 (2 studies) 7-90 days | LOW[a] due to risk of bias | RR 0.26 (0.1 to 0.7) | 98 per 1000 | 73 fewer per 1000 (from 29 fewer to 88 fewer) |
| PE | 368 (2 studies) 7-90 days | VERY LOW[b] due to risk of bias, imprecision | Peto OR 0.07 (0 to 4.01) | 7 per 1000 | 6 fewer per 1000 (from 7 fewer to 19 more) |
| Fatal PE | 303 (1 study) 7-90 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.59 (0.03 to 10.34) | 9 per 1000 | 4 fewer per 1000 (from 9 fewer to 75 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 153: Clinical evidence summary: IPCD (full leg) versus foot pump**

| 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 IPCD (full leg) versus foot pump (95% CI) |
| All-cause mortality | 149 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 1.22 (0.39 to 3.81) | 67 per 1000 | 15 more per 1000 (from 41 fewer to 187 more) |
| DVT (symptomatic and asymptomatic) | 124 (1 study) | VERY LOW[a,b,c] due to risk of bias, | RR 0.31 (0.11 to 0.89) | 210 per 1000 | 145 fewer per 1000 (from 23 fewer to 187 fewer) |

| 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 IPCD (full leg) versus foot pump (95% CI) |
| | 8 days | indirectness, imprecision | | | |
| Major bleeding | 149 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Peto OR 7.49 (0.15 to 377.48) | 0 per 1000 | Not estimable[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 Could not be calculated as there were no events in the comparison group

**Table 154: Clinical evidence summary: IPCD (below knee) versus foot pump**

| 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 IPCD (below knee) versus foot pump (95% CI) |
| DVT (symptomatic and asymptomatic) | 117 (1 study) up to 14 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.17 (0.02 to 1.76) | 44 per 1000 | 36 fewer per 1000 (from 43 fewer to 31 more) |
| PE | 117 (1 study) 2 months | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.18 (0 to 9.51) | 15 per 1000 | 12 fewer per 1000 (from 15 fewer to 110 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 155: Clinical evidence summary: IPCD (full leg) + AES (undefined) versus no 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 IPCD full leg + AES versus no prophylaxis (95% CI) |
| All-cause mortality | 96 (1 study) up to 3 weeks | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 47 fewer to 47 more)[d] |
| DVT (symptomatic and asymptomatic) | 96 (1 study) up to 3 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 4 (0.77 to 20.69) | 31 per 1000 | 94 more per 1000 (from 7 fewer to 615 more) |
| PE | 96 (1 study) up to 3 weeks | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.22 (0 to 14.26) | 16 per 1000 | 12 fewer per 1000 (from 16 fewer to 169 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 156: Clinical evidence summary: Continual passive motion + UFH versus UFH**

| 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 Continual passive motion + UFH versus UFH (95% CI) |
| All-cause mortality | 227 (1 study) 3 months | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 17 fewer to 17 more)[d] |
| DVT (symptomatic and asymptomatic) | 227 (1 study) 3 months | MODERATE[a] due to risk of bias | RR 0.14 (0.05 to 0.4) | 250 per 1000 | 215 fewer per 1000 (from 150 fewer to 237 fewer) |
| PE | 227 | VERY LOW[a,b] | Not | Not | 0 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 Continual passive motion + UFH versus UFH (95% CI) |
| | (1 study)<br>3 months | due to risk of bias, imprecision | estimable[c] | estimable[c] | (from 17 fewer to 17 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 Could not be calculated as there were no events in the intervention or comparison group
d Risk difference calculated in Review Manager

**Table 157: 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 Control | Risk difference with UFH versus no prophylaxis (95% CI) |
| All-cause mortality | 360<br>(3 studies)<br>up to 3 months | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.32<br>(0.06 to 1.64) | 24 per 1000 | 17 fewer per 1000<br>(from 23 fewer to 16 more) |
| DVT (symptomatic and asymptomatic) | 360<br>(3 studies)<br>up to 3 months | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.47<br>(0.17 to 1.26) | 68 per 1000 | 36 fewer per 1000<br>(from 57 fewer to 18 more) |
| PE | 360<br>(3 studies)<br>up to 3 month | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.17<br>(0.01 to 2.88) | 10 per 1000 | 8 fewer per 1000<br>(from 10 fewer to 18 more) |
| Fatal PE | 206<br>(1 study)<br>7-90 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 1.24<br>(0.08 to 20.32) | 9 per 1000 | 2 more per 1000<br>(from 8 fewer to 144 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 158: Clinical evidence summary: UFH versus IPCD (full leg)**

| 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 IPCD (full leg) versus UFH (95% CI) |
| All-cause mortality | 281 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 1.03 (0.09 to 11.18) | 11 per 1000 | 0 fewer per 1000 (from 10 fewer to 108 more) |
| DVT (symptomatic and asymptomatic) | 281 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 1.23 (0.3 to 5.05) | 33 per 1000 | 6 more per 1000 (from 19 fewer to 107 more) |
| PE | 281 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 17 fewer to 17 more)[e] |
| Fatal PE | 281 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Peto OR 2.20 (0.11 to 42.32) | 11 per 1000 | 6 more per 1000 (from 5 fewer to 178 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

d Could not be calculated as there were no events in the intervention or comparison group

e Risk difference calculated in Review Manager

**Table 159: Clinical evidence summary: UFH versus IPCD (full leg) + AES (undefined)**

| 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 IPCD full leg + AES versus UFH (95% CI) |

| 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 IPCD full leg + AES versus UFH (95% CI) |
| All-cause mortality | 76 (1 study) up to 3 weeks | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 52 fewer to 52 more)[d] |
| DVT (symptomatic and asymptomatic) | 76 (1 study) up to 3 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.18 (0.02 to 1.55) | 125 per 1000 | 102 fewer per 1000 (from 123 fewer to 69 more) |
| PE | 76 (1 study) up to 3 weeks | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 52 fewer to 52 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 Could not be calculated as there were no events in the intervention or comparison group

d Risk difference calculated in Review Manager

**Table 160: Clinical evidence summary: LMWH (standard dose; standard duration) + IPCD (below knee) versus IPCD (below knee)**

| 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) + IPCD versus IPCD (95% CI) |
| All-cause mortality | 120 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 1.14 (0.44 to 2.95) | 117 per 1000 | 16 more per 1000 (from 65 fewer to 228 more) |
| DVT (symptomatic and asymptomatic) | 120 (1 study) time-point not | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 0.75 (0.18 to 3.21) | 67 per 1000 | 17 fewer per 1000 (from 55 fewer to 147 more) |

| 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) + IPCD versus IPCD (95% CI) |
| | reported | | | | |
| PE | 120 (1 study) time point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 32 fewer to 32 more)[e] |
| Major bleeding | 120 (1 study) time point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 32 fewer to 32 more)[e] |
| Fatal PE | 120 (1 study) time point not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 2 (0.38 to 10.51) | 33 per 1000 | 33 more per 1000 (from 21 fewer to 317 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 if the outcome does not fit the protocol
d Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

**Table 161: 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 Control | Risk difference with LMWH versus UFH (95% CI) |
| All-cause mortality | 344 (1 study) 14 days | LOW[a] due to imprecision | Peto OR 7.52 (0.47 to 120.72) | 0 per 1000 | Not estimable[b] |
| DVT (symptomatic and asymptomatic) | 265 (1 study) | MODERATE[a] due to imprecision | RR 0.7 (0.51 to 0.97) | 441 per 1000 | 132 fewer per 1000 (from 13 fewer to 216 fewer) |

| 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 versus UFH (95% CI) |
| | 10-14 days | | | | |
| PE | 265 (1 study) 14 days | LOW[a] due to imprecision | Peto OR 7.8 (0.15 to 393.69) | 0 per 1000 | Not estimable[b] |
| Major bleeding | 344 (1 study) 14 days | MODERATE[a] due to imprecision | Peto OR 3.92 (0.78 to 19.63) | 6 per 1000 | 17 more per 1000 (from 1 fewer to 97 more) |
| Fatal PE | 344 (1 study) 14 days | LOW[a] Due to imprecision | Not estimable[c] | Not estimable[c] | 0 more per 1000 (from 113 fewer to 113 more)[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 Could not be calculated as there were no events in the comparison group
c Could not be calculated as there were no events in the intervention or comparison group
d Risk difference calculated in Review Manager

**Table 162: Clinical evidence summary: LMWH (high dose; standard duration) versus IPCD (below knee)**

| 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 versus IPCD (95% CI) |
| All-cause mortality | 442 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 more per 1000 (from 88 fewer to 88 more)[d] |
| DVT (symptomatic and asymptomatic) | 442 (1 study) 30 days | LOW[a,b] due to risk of bias, imprecision | Peto OR 0.24 (0.05 to 1.07) | 27 per 1000 | 20 fewer per 1000 (from 25 fewer to 2 more) |
| PE | 442 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.03 (0.06 to 16.48) | 4 per 1000 | 0 more per 1000 (from 4 fewer to 64 more) |

| 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 versus IPCD (95% CI) |
| | 30 days | | | | |
| Major bleeding | 442<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 1.03<br>(0.26 to 4.06) | 18 per 1000 | 1 more per 1000<br>(from 13 fewer to 55 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 163: Clinical evidence summary: LMWH (high dose; standard duration) versus (IPCD, undefined + AES, undefined) or FID**

| 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 versus (IPCD + AES) or FID (95% CI) |
| All-cause mortality | 202<br>(1 study)<br>time-point not reported | VERY LOW[a,b,c]<br>due to risk of bias, imprecision, indirectness | Not estimable[c] | Not estimable[c] | 0 per 1000<br>(from 202 fewer to 202 more)[d] |
| DVT (symptomatic and asymptomatic) | 202<br>(1 study)<br>time-point not reported | VERY LOW[a,b,c]<br>due to risk of bias, imprecision, indirectness | Peto OR 0.34<br>(0.03 to 3.40) | 24 per 1000 | 16 fewer per 1000<br>(from 24 fewer to 54 more) |
| PE | 202<br>(1 study)<br>time-point not reported | VERY LOW[a,b,c]<br>due to risk of bias, imprecision, indirectness | Not estimable[c] | Not estimable[c] | 0 per 1000<br>(from 202 fewer to 202 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 Control | Risk difference with LMWH versus (IPCD + AES) or FID (95% CI) |

c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

**Table 164: Clinical evidence summary: LMWH (high dose; standard duration) versus delayed LMWH (high dose; standard duration) + foot pump**

| 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 versus LMWH + foot pump (95% CI) |
| All-cause mortality | 200 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 per 1000 (from 194 fewer to 194 more)[e] |
| DVT (symptomatic and asymptomatic) | 200 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.53 (0.69 to 3.43) | 87 per 1000 | 46 more per 1000 (from 27 fewer to 212 more) |
| PE | 200 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.94 (0.49 to 128.04) | 0 per 1000 | Not estimable[c] |
| Fatal PE | 200 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 per 1000 (from 194 fewer to 194 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 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 Control | Risk difference with LMWH versus LMWH + foot pump (95% CI) |
| c Could not be calculated as there were no events in the comparison group<br>d Could not be calculated as there were no events in the intervention or comparison group<br>e Risk difference calculated in Review Manager | | | | | |

## 34.4 Economic evidence

**Published literature**

Two health economic studies were identified with the relevant comparison, and have been included in this review.[51,198] One of these two studies was previously included in CG92. [198] The two studies are summarised in the health economic evidence profiles below (Table 165 and Table 166) and the health economic evidence tables in appendix J.

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

**Table 165: Health economic evidence profile: VCF vs IPCD**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Carter Chiasson 2009[51] [(Canada)] | Partially applicable [(a)] | Potentially serious limitations [(b)] | **-Study design:** cost-utility analysis using decision analytic modelling.<br>**-Population:**<br>Adult (>/= 15 years)Trauma patients with severe injuries admitted to the ICU who were believed to have a contraindication to pharmacological VTE prophylaxis for up to 2 weeks because of a risk of major bleeding.<br>**-Interventions**<br>1. Pneumatic compression devices (IPCD) and expectant management alone during the first 2 weeks.<br>2. IPCD as well as weekly Serial Doppler ultrasound (SDU) screening for the duration of hospitalisation beginning in the first week of ICU admission. **(results not reported here)**<br>**3.** Prophylactic insertion of vena-cava filter (VCF). | 3 vs 1<br>£975 | 3 vs 1<br>0.0 QALYs | IPCD less costly | A wide range of one-way sensitivity analyses was undertaken. None of the SAs changed the conclusion |

*Abbreviations: ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IPCD: pneumatic compression device; QALY: quality-adjusted life years; RCT: randomised controlled trial; SAs: sensitivity analyses; VCF: vena-cava filter; VTE: venous thromboembolism.*

*(a) Uncertainty regarding the applicability of unit costs from Canada, in 2007 to current NHS context. The discount used is 5% for both costs and outcomes; however, this was tested in a sensitivity analysis with a range of 0-6%. It is not clear which utility measure was used to derive the utility values used in the model.*

*(b) The health states included in the long term of the model does not seem to include CTEPH as a complication of PE. Baseline risks as well as relative effectiveness are based on the results of an observational cohort and single RCT so by definition, not reflective of all the evidence in this area. Both local and national unit costs were used in the analysis, so may not be generalisable. Utility values were not tested in sensitivity analysis.*

**Table 166: Health economic evidence profile: LMWH (low dose) vs UFH (low dose)**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Lynd 2007[198] ([Canada]) | Partially applicable [(a)] | Potentially serious limitations [(b)] | **- Study design:** cost-consequences analysis using decision analytic modelling.<br>**- Population:**<br>Patients with major trauma (trauma score of =>9)<br>**- Interventions:**<br>1. UFH 5000 units once daily.<br>2. LMWH (enoxaparin 30 mg once daily). | 2 vs 1<br><br>£47 | 2 vs 1<br><br>**LYG:**<br>130 life-years lost per 1000<br><br>**DVT:**<br>86 DVTs averted per 1000<br><br>**PE**:<br>18 PEs averted per 1000 patients<br><br>**MB**:<br>18 more MB events per 1000 patients<br><br>**Deaths:**<br>7 fewer deaths per 1000 patients | 2 vs 1<br><br>**LYG:** Dominated (more costly and less effective)<br><br>**DVT**:<br>£553 per DVT averted<br><br>**PE:**<br>£2,611 per PE averted<br><br>**MB:**<br>Dominated (more costly and less effective)<br>**Deaths**:<br>£6,714 per death averted | Probabilistic and deterministic (one-way and two-way) sensitivity analyses were conducted. The model results were robust to all changes. |

*Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial; UFH: unfractionated heparin.*

*a) Uncertainty regarding the applicability of unit costs from Canada, in 2003 to current NHS context. The discount used is 5% for outcomes; however, this was tested in a sensitivity analysis with a range of 3-7%. QALYs were not used as outcome.*

*b) The health states included in the long term of the model do not include CTEPH and PTS. Baseline risks as well as relative effectiveness are based on the results of a single RCT (Geerts 1996[112]) so by definition, not reflective of all the evidence in this area. Both local and national unit costs were used in the analysis, so may not be generalisable.*

## 34.5 Evidence statements

### Clinical

#### Mechanical prophylaxis

When IPCD (full leg) was compared to no prophylaxis, evidence from two studies (n=368) showed there was a clinical benefit of IPCD for DVT. And suggested benefit for all other outcomes including all-cause mortality, PE and fatal PE. However the non-DVT outcomes were all associated with imprecision. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

The study comparing IPCD (full leg) in combination with AES with no prophylaxis (n=96) found a possible clinical harm of IPCD + AES for DVT, and a possible clinical benefit for PE. However there was imprecision associated with these results. There was no clinical difference for all-cause mortality. The quality of the evidence was very low due to risk of bias and imprecision.

For the comparison of IPCD (full leg) versus foot pump, evidence from one study (n=149) suggested clinical benefit of IPCD for DVT, but a possible clinical harm for major bleeding, however there was imprecision around these results. There was no clinical difference in terms of all-cause mortality. For below knee IPCD compared to foot pump, the evidence from another single study (n=117) demonstrated a possible clinical benefit for IPCD for both DVT and PE, but there was imprecision around the results. The quality of the evidence for both comparisons ranged from very low to low due to risk of bias and imprecision.

#### *Mechanical versus pharmacological prophylaxis*

When IPCD (full leg) was compared to UFH (single study, n=281), there was a suggested clinical benefit of IPCD for fatal PE, and no clinical difference for all other reported outcomes including all-cause mortality, DVT and PE. However there was uncertainty surrounding these results. The quality of the evidence was very low due to risk of bias, imprecision and indirectness.

For the comparison of IPCD (full leg) in combination with AES versus UFH (single study, n=76), there was a possible clinical harm of IPCD in combination with AES for DVT, and no clinical difference for all-cause mortality or PE. However this evidence was very low quality due largely to the very serious imprecision surrounding the effect estimates.

For the comparison of continual passive motion in combination with UFH versus UFH alone (single study, n=227), there was clinical benefit of continual passive motion for DVT, and no clinical difference for all-cause mortality and PE. The quality of the evidence ranged from very low to moderate due to risk of bias and imprecision.

When LMWH (standard dose) in combination with IPCD (below-knee) was compared to IPCD (below-knee), evidence from one study (n=120) suggested a clinical benefit of LMWH for DVT, and a suggested clinical harm for fatal PE. There was no clinical difference for all-cause mortality, PE and major bleeding. However for all results there was uncertainty around the effect estimates. The quality of the evidence was very low due to risk of bias, imprecision and indirectness.

When LMWH (high dose) was compared to IPCD (below-knee), evidence from one study (n=442) suggested clinical benefit of LMWH for DVT, however no clinical difference for all-cause mortality, PE and major bleeding. There was considerable uncertainty around all these results. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

The study comparing LMWH (high dose) to (IPCD in combination with AES) or FID (n=202) found a suggested clinical benefit of LMWH for DVT, and no clinical difference for all-cause mortality and PE.

There was considerable uncertainty around all these results. The quality of the evidence was very low due to risk of bias, imprecision and indirectness.

For the comparison of LWMH (high dose) versus delayed LMWH (high dose) in combination with foot pump, the evidence from one study (n=200) suggested a possible clinical harm for LMWH for both DVT and PE, and no clinical difference for all-cause mortality and fatal PE, however all these results had considerable uncertainty.

***Pharmacological prophylaxis***

For the comparison of UFH versus no prophylaxis, evidence from 3 studies (n=360) suggested clinical benefit of UFH for all-cause mortality, DVT and PE. However these results were very seriously imprecise and associated with both no difference and harm as well. No clinical difference was found for fatal PE. The quality of the evidence was very low due to risk of bias and imprecision.

For the comparison of LWMH (high dose) versus UFH, the evidence from one study (n=344) suggested a possible clinical harm of LMWH for all-cause mortality, PE and major bleeding, however the evidence was very imprecise and also consistent with no difference and possible benefit. However there was a possible clinical benefit of LMWH for DVT, although this was also consistent with no difference. There was no clinical difference in terms of fatal PE. The quality of the evidence ranged from low to moderate due to imprecision.

**Economic**

One cost–utility analysis found that in trauma patients with severe injuries admitted to the ICU, pneumatic compression devices and expectant management alone was less costly and equally effective, compared to prophylactic insertion of vena-cava filter for VTE prophylaxis. This analysis was assessed as partially applicable with potentially serious limitations.

One cost-consequences analysis found that in patients with major trauma low molecular weight heparin (low dose) was more costly (£47 more per patient) and had 0.086 fewer DVT events per patient, 0.0018 fewer PE events per patient and 0.007 fewer deaths per patient but 0.0018 more major bleeding events per patient and 0.013 fewer life-years gained per patient compared to unfractionated heparin (low dose) for VTE prophylaxis. This analysis was assessed as partially applicable with potentially serious limitations.

## 34.6 Recommendations and link to evidence

| | |
|---|---|
| **Recommendations** | **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]**<br><br>**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]**<br><br>**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]** |
| **Research** | **None** |

| recommendation | |
|---|---|
| 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.<br><br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br><br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Ten studies were included in this review. Four were included in the previous guideline (CG92) and six were new studies. A total of thirteen comparisons were identified from the ten included studies, evaluating mechanical (IPCD, AES, continual passive motion and foot pump) and pharmacological (UFH and LMWH) interventions for VTE prophylaxis.<br><br>The committee discussed that the generalisability of evidence from studies to individual patients should be considered. The trials included moderate to severe trauma patients with a wide range of ISS levels reported (if at all) and a variety of injuries, with the more severe patients usually managed in specialised trauma centres. There is a range of risks for VTE and bleeding, depending on the type, location and severity of the injuries. The majority of the evidence was downgraded due to risk of bias based on inadequate randomisation and allocation concealment. Much of the evidence was further downgraded due to imprecision. In cases where major bleeding was not adequately defined, the evidence from these studies was also downgraded for indirectness of the outcome. |
| Trade-off between clinical benefits and harms | The committee noted that the high event rate for DVT and PE in this population compared to some of the other review populations is expected. This tallies with clinical experience; it is common for ICU populations to experience higher rates of DVT and PE. Therefore clinicians are likely to be comfortable with the idea of administering VTE prophylaxis in this population. The committee noted that the trauma population are likely to have significant immobilisation due to the nature of their injuries which would contribute to an increased risk for VTE.<br><br>Evidence was identified for both mechanical and pharmacological prophylaxis both compared to each other and to no VTE prophylaxis. When considering the evidence for mechanical prophylaxis, the committee noted that the evidence showed some possible clinical benefits of IPCD alone or in combination with AES for the outcomes of all-cause mortality, DVT and PE, however there was uncertainty around these results consistent with no difference, or harm. There were seven comparisons of mechanical versus pharmacological prophylaxis. This evidence demonstrated conflicting findings, with some suggesting clinical benefits of mechanical prophylaxis or combined mechanical and pharmacological prophylaxis for DVT, PE and fatal PE, and other evidence demonstrating clinical benefits of pharmacological prophylaxis for DVT.<br><br>The committee discussed that for the major trauma population, the risk of bleeding is high, and therefore mechanical prophylaxis may be preferable. It was also noted that AES are not always practical in the major trauma population, due to the nature of the injuries which may prevent AES from being worn (for example injuries involving broken legs). The committee discussed different prophylaxis strategies including immediate combined mechanical and pharmacological prophylaxis or initial mechanical and then switching to pharmacological once bleeding risk had minimised. While the review sought to find any differences between the effectiveness of IPCD |

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| | and foot-pumps, in practice foot-pumps are understood to be a subset (type) of intermittent pneumatic compression device, specifically shaped for the foot only. The committee considered that the evidence did not clearly demonstrate clinical superiority of half- or full-leg based IPCD compared to foot pumps and therefore decided it was reasonable to group all such devices under the more general term of intermittent pneumatic compression. The committee concluded that mechanical prophylaxis such as IPCD and foot pumps should be recommended as initial treatment, until the risk of bleeding is reduced, at which time the risk of bleeding should be weighed against the risk of VTE. Given the lack of evidence for AES alone and the practical issues surrounding its use, the committee concluded that AES would not be recommended.<br><br>There were two pharmacological prophylaxis only comparisons. When UFH was compared to no prophylaxis, possible clinical benefits of UFH were seen for all-cause mortality, DVT and PE. However, when UFH was compared to LMWH, the evidence was mixed and therefore the committee considered that there was insufficient evidence to specify which type of pharmacological prophylaxis was most effective for this population. It was highlighted that if necessary (for example reoperation) anticoagulation with UFH can be reversed, unlike with LMWH or fondaparinux. The committee concluded that pharmacological prophylaxis should be considered for major trauma patients, but did not specify which type of pharmacological prophylaxis should be used. The particular prophylaxis preparation used would need to be based on clinical judgement on consideration of the individual patient factors. The committee also discussed whether pharmacological prophylaxis should be given in addition to or as an alternative to mechanical prophylaxis, however it was agreed that this would need to depend on a clinical judgement taking into account the individual patient. |
| Trade-off between net clinical effects and costs | Two economic studies have been included in this review. One study comparing LMWH to UFH was previously included in CG92. The second study compared VCFs to IPCDs in trauma patients who have contraindications to pharmacological prophylaxis. Both studies were assessed as partially applicable with potentially serious limitations.<br><br>The committee discussed the economic evidence alongside the clinical evidence. It was acknowledged that the serious and major trauma populations are at very high risk of bleeding, hence mechanical prophylaxis options will have a more favourable benefit-harm balance, particularly in the early stages of the trauma event. The economic evidence presented supported the cost effectiveness of IPCD and showed that it was a cost saving option compared to VCFs in people who have contraindication to pharmacological prophylaxis. The committee considered that, based on the evidence presented and their collective clinical experience, the use of VCFs for primary prevention of VTE in this population is not a cost-effective use of resources. They also acknowledged that the removal of VCF incurs extra cost that has not been included in the economic evidence presented and this is likely to make VCFs even more costly. Hence, the committee chose to recommend against their use for the purpose of primary VTE prevention in this population. For people at low risk of major bleeding, the committee considered that the benefit of pharmacological prophylaxis in the prevention of VTE is likely to outweigh their risks. Therefore, the committee considered the addition of pharmacological prophylaxis in this group to be a cost-effective use of resources and likely to be off-set through the prevention of costly VTE events. |
| Other considerations | It was noted that the studies included in this review include populations with varying degrees of injury severity. Initially the committee considered including only those papers with patients with major trauma defined as Injury Severity Score ≥16.[15] However in keeping in line with the NICE Major Trauma guideline (https://www.nice.org.uk/guidance/ng39) this definition was extended to include major trauma by definition of included study. The committee discussed that in the UK context having an ISS of ≥9 gets patient details entered onto TARN (trauma |

| | |
|---|---|
| | audit and research network). Once the ISS is getting into the high teens this represents multi-system injuries.<br><br>The committee highlighted that reassessment of VTE and bleeding risk needed to happen on an at least daily basis in this population due to the nature of their injuries and evolving risk profile.<br><br>The committee also considered the use of vena caval filters, however due to the lack of clinical evidence and the presence of economic evidence demonstrating it not to be cost effective it was decided not to recommend this method of prophylaxis.<br><br>For people undergoing neurosurgery as a result of a head injury see the recommendations relating to cranial surgery insection 32.6. |

# 35 Abdominal surgery (excluding bariatric surgery)

## 35.1 Introduction

This section covers major abdominal surgery, including both open and laparoscopic surgery. Major abdominal surgery covers inpatients undergoing gastrointestinal, gynaecological and urological surgery.

Gastrointestinal surgery by its nature is heterogeneous in terms of the age of patients, the pathological conditions being dealt with and organs and systems operated upon. There remain a variety of procedures retained within this category that are specialisations in themselves. These include upper gastrointestinal surgery and lower intestinal surgery (or coloproctology). Factors that may alter the risk of VTE:

- Patients having surgery for cancer will have an increased risk of developing a DVT or pulmonary embolism.
- Patients having emergency procedures are often elderly and will consequently be at higher risk of developing a DVT or pulmonary embolism.
- Some patients having emergency procedures may already be using anticoagulation or antiplatelet therapy. This needs to be considered when deciding on the method of VTE prophylaxis.

Open gynaecological surgery includes abdominal and vaginal surgery, excluding caesarean section. Factors that may alter the risk of VTE:

- Patients may be using hormonal contraception and hormone replacement therapy, which will increase their risk of developing a DVT or pulmonary embolism.
- Patients having surgery for cancer will have an increased risk of developing a DVT or pulmonary embolism.

Open urological surgery is divided into two major groups: pelvic cancer surgery and renal surgery. Patients undergoing these procedures are usually between the ages of 65 and 75.

Factors that may alter the risk of VTE:

- Many urological surgery patients have spinal and epidural anaesthesia. This may reduce the risk of developing a DVT.
- Renal surgery procedures may involve division of the renal vein where it drains into the inferior vena cava. This could potentially increase the risk of VTE.

There are no specific factors that increase the risk of bleeding or the hazard associated with it in open gastrointestinal, gynaecological or urological surgery. There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in these surgeries.

Laparoscopic surgery is used in gastrointestinal, gynaecological and urological surgery. Specific considerations apply to it in all these specialities. Factors that may alter the risk of VTE:

- There is some concern that the increased pressure in the peritoneal cavity during laparoscopic surgery causes venous stasis which may increase VTE risk.
- Some laparoscopic procedures tend to last longer than open procedures.
- Being less invasive, most people will make a quicker return to mobility following laparoscopic procedures compared to open procedures.

Factors that may alter the risk of bleeding:

- Laparoscopic procedures may be associated with less bleeding than open surgery.

- Bleeding may make laparoscopic surgery difficult or impossible and result in the need for conversion to open surgery.

There are no other special factors that may affect the choice, and use of, specific methods of VTE prophylaxis in laparoscopic surgery.

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

For full details see review protocol in appendix C.

**Table 167: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) undergoing abdominal surgery (including gastrointestinal, gynaecological, urological) who are admitted to hospital, and outpatients post-discharge |
| **Interventions** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological (no minimum duration):<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists: warfarin (variable dose), acenocoumarol (all doses), phenindione (all doses)<br>• Fondaparinux (all doses)<br>• Apixaban (all doses)<br>• Dabigatran (all doses) |

| | |
|---|---|
| | • Rivaroxaban (all doses)<br>• Aspirin (up to 300mg)*<br><br>*off-licence |
| **Comparisons** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge) (NMA outcome)<br>• Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) (NMA outcome)<br>• Pulmonary embolism (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE (NMA outcome)<br>• Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (NMA outcome)<br>• 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<br><br>Important outcomes:<br>• 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<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

## 35.3 Clinical evidence

Sixty-seven studies in 69 papers were included in the review these are summarised in Table 168 below. Sixty-two studies were previously included in the previous guideline (CG92);[5, 317, 316, 292, 293, 6, 19, 37, 38, 44, 29, 30, 28, 25 ,26, 24, 22, 42, 50, 54, 56, 55 ,57 ,58, 92, 102, 109 ,110, 118, 120 ,131 ,138, 136, 156, 160, 159, 169, 175-177, 193, 202, 204, 210,

[232, 235, 238, 239, 236, 245, 250, 251, 268, 272, 284, 286, 291, 290, 294, 303, 137 ,302] and five studies were added to the update; [111, 260, 223, 158, 273, 137]. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 169, Table 170, Table 171, Table 172, Table 173, Table 174, Table 175, Table 176, Table 177, Table 178, Table 179, Table 180, Table 181, Table 182, Table 183, Table 184, Table 185, Table 186, Table 187, Table 188, Table 189, Table 190, Table 191, Table 192, Table 193, Table 194, Table 195, Table 196, Table 197, Table 198, Table 199, Table 200, Table 201, Table 202, Table 203, Table 204, Table 205, Table 206, Table 207). 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.

Based on the current review protocol, six systematic reviews that were included in CG92 were excluded but checked for references. The studies from all of one systematic review[11] were excluded due to having the incorrect intervention. Some of the studies from five systematic reviews[7, 61, 167, 217, 256] were excluded due to having incorrect population, intervention or comparisons. For this update, data from the original papers, rather than systematic review data, was used.

A large amount of people undergo major abdominal surgery, and where evidence for other populations relating to torso surgery (e.g. thoracic surgery and cardiac surgery) is lacking, the committee agreed to consider major abdominal surgery as indirect evidence. Therefore in order to compare the clinical effectiveness data of multiple possible interventions, it was proposed that a network meta-analysis be carried out on the outcome data for DVT, PE and major bleeding in this population. These analyses provide estimates of effect (with 95% credible intervals) for each intervention compared to one another and compared to a single baseline risk (in this case the baseline treatment was no prophylaxis or in the case of the major bleeding outcome a combination of no prophylaxis and mechanical prophylaxis). These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. For full details on the NMA methodology and results, please see appendix M.

**Table 168: Summary of systematic reviews included in the review**

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Agnelli 2005[1] | Intervention (n=1433):<br>Fondaparinux (2.5 mg, 1 x daily).<br>Duration: started 6 hours post-op and repeated daily for 5-9 days.<br><br>Comparison (n=1425):<br>LMWH, standard dose, (dalteparin, 5000U, 1 x daily).<br>Duration: started 2 hours before operation (2500U), and then given 12 hours later (2500U). 5000 units given once daily thereafter for 5-9 days. | n=2858<br><br>People having high risk abdominal surgery (duration >45 minutes)<br><br>Age >40 years<br><br>Male and female (1584:629)<br><br>Cancer 67.9%<br><br>Multiple countries (131 hospitals in 22 countries) | All-cause mortality (32 days)<br><br>DVT (32 days): confirmed by bilateral venography<br><br>Symptomatic pulmonary embolism (32 days): confirmed by high probability lung scan, pulmonary angiography, helical computed tomography or autopsy<br><br>Major bleeding (7-11 days): fatal, retroperitoneal, | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | intracranial, intraspinal, or involved any other critical organ, bleeding leading to reoperation or intervention, or a bleeding index of 2.0 or more<br><br>Fatal PE (32 days): confirmed by autopsy | |
| Allan 1983[5] | Intervention (n=97):<br>AES, length not stated. Duration: evening before operation until 7 days post-op<br><br>Comparison (n=103): no VTE prophylaxis | n=200<br><br>People having abdominal surgery (duration >30 minutes)<br><br>Age >40 years<br>Male and female<br><br>UK | DVT (7 days): confirmed by fibrinogen uptake test | |
| Allen 1978[6] | Intervention (n=30):<br>UFH (5000U 2 x daily)<br>Duration: started 2 hours before surgery, until discharge<br><br>Comparison (n=30):<br>No VTE prophylaxis | n=60<br><br>People undergoing urologic surgery (transurethral prostatectomy)<br><br>Age (average): intervention 71.9, comparison 71.2<br><br>UK | All-cause mortality (time-point not reported)<br><br>Major bleeding (time-point not reported): defined as requiring a transfusion of two units of blood | |
| Bejjani 1983[19] | Intervention (n=17):<br>UFH (5000U 2 x daily)<br>Duration: started 3 hours before surgery or on admission, for 2 days<br><br>Comparison (n=17):<br>No VTE prophylaxis (placebo, 2ml saline 2 x daily).<br>Duration: started 3 hours before surgery or on admission, for 2 days | n=34<br><br>People undergoing urologic surgery<br><br>Cancer = 38%<br><br>United States | PE (postoperatively): confirmed by ventilation perfusion lung scan<br><br>Major bleeding (postoperatively): defined as bleeding requiring a transfusion of 2 units | |
| Bergqvist | Intervention (n=46): | n=97 | All-cause mortality | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| 1980[29] | UFH (5000U, 2 x daily)<br>Duration: started 2 hours before surgery or on admission, for 5 days<br><br>Comparison (n=51):<br>No VTE prophylaxis | People having general surgery (abdominal surgery 56.7%, urologic surgery 38.1%)<br><br>Male and female (63:34)<br>Age >51 years<br><br>22% malignant disease<br><br>Sweden | (up to 7 days)<br><br>DVT (up to 7 days): confirmed by I-fibrinogen test<br><br>Fatal PE (up to 7 days): method of confirmation not reported | |
| Bergqvist 1986 [25,26] | Intervention (n=215):<br>LMWH, standard dose (dalteparin, 5000U, 1 x daily)<br>Duration: started 2 hours before operation, for 5-7 days<br><br>Comparison (n=217):<br>UFH 5000U 2 x daily<br>Duration: started 2 hours before operation, for 5-7 days | n=432<br><br>People having general surgery (gastric surgery 7.9%, biliary tract surgery 29.6% , colonic surgery 37%, rectal surgery 18.2%, pancreatic surgery 0.5%, other 6.7%)<br><br>Age > 40<br>45% malignancies<br><br>Sweden | All-cause mortality (30 days)<br><br>DVT (7 days): confirmed by I-labelled fibrinogen uptake test<br><br>Major bleeding (30 days): defined as bleeding requiring reintervention | |
| Bergqvist 1988[30] | Intervention (n=505):<br>LMWH, standard dose (dalteparin 5000U, 1 x daily).<br>Duration: started the evening before surgery, for 5-8 days<br><br>Comparison (n=497):<br>UFH (5000U), 2 x daily (the first injection contained placebo)<br>Duration: started the evening before surgery, for 5-8 days | n=1002<br><br>People having general abdominal surgery (gastric surgery 10%, biliary tract surgery 8.6% , colonic surgery 56.6%, rectal surgery 17.6%, pancreatic surgery 2.4%, other 4.6%)<br><br>Median duration: LMWH = 120 minutes, UFH = 125 minutes<br><br>Aged > 41 years<br>Male and female (488:514)<br><br>Sweden | All-cause mortality (30 days)<br><br>DVT (7 days days): confirmed by I-labelled fibrinogen uptake test<br><br>PE (30 days): confirmed by scintigraphy<br><br>Fatal PE (30 days): confirmed by autopsy | |
| Bergqvist 1995[24] | Intervention (n=1036):<br>LMWH, standard dose, (dalteparin, 5000U, 1 x | n=2070<br><br>People having abdominal | All-cause mortality (30 days post op): confirmed by autopsy | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | daily).<br>Duration: started 22 hours the day before surgery for 7 days postoperatively.<br><br><u>Comparison (n=1034):</u><br>LMWH, low dose (dalteparin, 2500U, 1 x daily).<br>Duration: started 22 hours the day before surgery for 7 days postoperatively. | surgery (duration, median: intervention 125 minutes, comparison 129 minutes)<br><br>Age > 40 years<br>Male and female (985:1085)<br><br>Sweden | DVT (7 days post-op): confirmed by fibrinogen uptake test<br><br>PE (30 days): confirmed by perfusion/ ventilation scintigraphy<br><br>Major bleeding (30 days post-op): defined as those leading to death or reoperation, or as being intracranial, intraocular or intraspinal | |
| Bergqvist 1996 [28] | <u>Intervention (n=39):</u><br>LMWH, standard dose (tinzaparin 3500U, 1 x daily). Duration: started post-operatively for >5 days<br><br><u>Comparison (n=41):</u><br>No VTE prophylaxis (placebo) | n=80<br><br>People having emergency abdominal surgery<br><br>Age >40 years<br>Males and females (37:43)<br><br>13.8% malignant disease<br><br>Sweden | All-cause mortality (30 days)<br><br>DVT (30 days): confirmed by FUT and venography<br><br>PE (30 days): method of confirmation not reported<br><br>Major bleeding (30 days): defined as bleeding requiring re-operation, transfusion or other intervention, leading to death or intraocular, intracranial or intraspinal bleeding | |
| Bergqvist 2002[21] | <u>Intervention (n=253):</u><br>extended LMWH, standard dose, (enoxaparin, 40mg, 1 x daily). Duration: started 10-14 hours before operation, then once daily for 25-31 days.<br><br><u>Comparison (n=248):</u> | n=501<br><br>People having abdominal surgery for cancer<br>Duration >45 minutes<br><br>Age >40 years<br><br>Male and female (200:132) | All-cause mortality (2 months)<br><br>DVT (25-31 days): confirmed<br>by bilateral venography<br><br>PE (3 months): confirmed by V/Q | AES were allowed |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | standard LMWH, standard dose, (enoxaparin, 40mg 1 x daily). Duration: started 10-14 hours before operation, then once daily for 6-10 days. Placebo for further 19-21 days. | Cancer 100%<br><br>Multiple countries | scan or angiogram<br><br>Major bleeding (3 months): bleeding resulting in death, a decrease in the haemoglobin concentration of 2 g per deciliter or more, or the transfusion of at least 2 units of blood; retroperitoneal, intracranial, or intraocular; resulted in a serious or life-threatening clinical event; or if surgical or medical intervention was required<br><br>Fatal PE (3 months): confirmed by autopsy | |
| Borstad 1988[37] | Intervention (n=105): LMWH, standard dose (dalteparin 5000U, 1 x daily)<br>Duration: started 1 hour preoperatively for 7 days<br><br>Comparison (n=110): UFH (5000U, 2 x daily)<br>Duration: started 1 hour preoperatively for 7 days | n= 215<br><br>People having major gynaecological surgery (laparotomy 52.6%, colposuspension 19.6%, vaginal repair 25.1%)<br>Duration >30 minutes<br><br>Age >40 years<br><br>Cancer 6%<br><br>Norway | DVT (7 days): confirmed by plethysmography and venography<br><br>PE (7 days): confirmed by clinical examination<br><br>Major bleeding (time-point not reported): defined as if the patient was reoperated, received blood transfusions or had prophylaxis stopped due to bleeding | |
| Borstad 1992[38] | Intervention (n=77): LMWH, low dose (dalteparin, 2500U, 1 x daily). Duration: started 1 hour before surgery for 7 days | n=152<br><br>People having major gynaecological surgery (laparotomy, colposuspension, vaginal repair) | All-cause mortality (1 month)<br><br>PE (1 month): confirmed by venography if | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison (n=75):<br>UFH (5000U 2 x daily).<br>Duration: started 1 hour before surgery for 7 days | Duration > 30 minutes<br><br>Age > 40 years<br><br>Norway | thromboembolic complications suspected from clinical examination<br><br>Major bleeding (5 days): defined as prophylaxis stopped because of bleeding, transfusions received, perioperative bleeding more than 1000 ml and pelvic haematoma | |
| Butson 1981[42] | Intervention (n=62):<br>IPCD, knee length<br>Duration: started immediately after anaesthesia and continued until fully ambulant (usually for 24-48 hours)<br><br>Comparison (n=57):<br>No VTE prophylaxis | n=119<br><br>People having general abdominal surgery<br><br>Age >20 years<br>Males and females (52:67)<br><br>Canada | DVT (discharge or 14 days): confirmed by fibrinogen scanning, venography, or autopsy<br><br>Fatal PE (discharge or 14-90 days): confirmed by autopsy | |
| Caen 1988[44] | Intervention (n=195):<br>LMWH, low dose (dalteparin, 2500U, 1 x daily)<br>Duration: 2 hours before operation until 7 days post-op<br><br>Comparison (n=190):<br>UFH (5000U, 2 x daily)<br>Duration: 2 hours before operation until 7 days post-op | n=385<br><br>People having major abdominal surgery<br>Duration of surgery >30 minutes<br><br>Age >40 years<br>Males and females (188:197)<br><br>France | All-cause mortality (30 days)<br><br>DVT (30 days): confirmed by I-fibrinogen uptake test<br><br>PE (30 days): method of confirmation not reported<br><br>Fatal PE (30 days): method of confirmation not reported | |
| Caprini 1983[48] | Intervention (n=38):<br>• AES, above knee<br>• IPCD, full leg<br>Duration: all patients wore bilateral AES preoperatively. IPCD was then applied prior to the onset of | n=77<br><br>People having general surgery (abdominal 64.9, orthopaedic 13%, neurologic 10.4%, genitourinary 10.4%, thoracic 1.3%) | DVT (time-point not reported):confirmed by venography, plethysmography and Doppler<br><br>PE (time-point not reported): | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | anaesthesia and maintained for at least 3 days postoperatively or until ambulant. When the IPCD was removed, AES was re-applied until discharge<br><br>Comparison (n=39):<br>AES, above knee.<br>Duration: started preoperatively, worn until discharge | Age 92.3% >40 years<br>Males and females (31:46)<br><br>16.7% malignant condition<br><br>United States | confirmed by angiography<br><br>Fatal PE (time-point not reported): method of confirmation not reported | |
| Chandhoke 1992[50] | Intervention (n=47):<br>IPCD, full length<br>Duration: applied intra-operatively and continued post-op for 5days or until patient became fully ambulant<br><br>Comparison (n=53):<br>VKA, (warfarin, variable dose).<br>Duration: started on the night of the operation, until discharge | n=100<br><br>People having urological surgery (radical prostatectomy 81%, radical cystectomy 9%, other pelvic surgery 3%, kidney surgery 7%)<br><br>Duration of surgery >2 hours<br><br>Age (mean, SD): intervention, 67.5 (7.1), comparison, 66.1 (6.4)<br><br>Male and Female (99:1)<br><br>Cancer 99%<br><br>United States | All-cause mortality (1-2 weeks)<br><br>DVT (5 days): confirmed by venography and ultrasound<br><br>PE (1-2 weeks): confirmed by venography and ultrasound | |
| Clarke-Pearson 1983 [54] | Intervention (n=88):<br>UFH (5000U, 2 x daily)<br>Duration: 2 hours before surgery, for 7 days<br><br>Comparison (n=97):<br>No VTE prophylaxis | n=185<br>People having gynaecological malignancy surgery<br><br>Age >20 years<br>Female<br><br>Cancer 100%<br><br>United States | DVT (42 days): confirmed by fibrinogen counting, impedance plethysmography and venography<br><br>PE (42 days): confirmed by ventilation-perfusion scanning and/or pulmonary arteriography<br><br>Fatal PE (42 days): confirmed at autopsy | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Clarke-Pearson 1984A[55] | Intervention (n=97): IPCD, below knee. Duration: applied at time of anaesthesia, until discharge from recovery room or for 1 day<br><br>Comparison (n=97): No VTE prophylaxis | n=194<br><br>People having major surgery for gynaecologic malignancies Duration of surgery (mean): 233 minutes<br><br>Female<br><br>Cancer 100%<br><br>United states | DVT (42 days): confirmed by I-labelled fibrinogen counting and impedance plethysmography and ascending venography<br><br>PE (42 days): ventilation perfusion lung scanning, and pulmonary arteriography<br><br>Fatal PE (42 days): confirmed by autopsy | |
| Clarke-Pearson 1984B[57] | Intervention (n=55): IPCD, below knee Duration: applied at time of anaesthesia for 5 days<br><br>Comparison (n=52): No VTE prophylaxis | n=107<br><br>People having major surgery for gynaecologic malignancies Duration of surgery >85 minutes<br><br>Age >20 years<br>Female<br><br>Cancer 100%<br><br>United states | All-cause mortality (42 days)<br><br>DVT (42 days): confirmed by I-fibrinogen counting and impedance plethysmography<br><br>PE (42 days): ventilation perfusion lung scanning, and pulmonary arteriography | |
| Clarke-Pearson 1993[56] | Intervention (n=107): UFH (5000U), 3 x daily Duration: started 16 hours before surgery (3 doses given preoperatively), for 7 days, until fully ambulated or until discharge<br><br>Comparison (n=101): IPCD, below knee. Duration: applied at induction of anaesthesia, for 5 days, until fully ambulant or until discharge | n=208<br><br>People having gynaecologic oncology surgery Duration >80 minutes<br><br>Age >22 years<br>Female<br><br>Cancer 76.4%<br><br>United States | DVT (until discharge): confirmed by fibrinogen uptake test, impedance plethysmography, duplex Doppler ultrasound and ascending contrast venography<br><br>PE (30 days): ventilation perfusion lung scanning and pulmonary arteriography | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Coe 1978[58] | Intervention 1 (n= 28): UFH (5000 U, 2 x daily) Duration: 2 hours before surgery, until discharge<br><br>Intervention 2 (n=29): Intermittent pneumatic compression device (IPCD), calf length. Duration: applied after induction of anaesthesia until discharge<br><br>Comparison (n=24): No VTE prophylaxis (control group, no further details reported) | n=81<br><br>People undergoing urologic surgery Duration of surgery (mean) 234 minutes<br><br>Age (mean, SD): intervention 1 = 63 (16) intervention 2 = 55 (11), control = 51 (18) Gender not reported<br><br>United States | DVT (until discharge): confirmed by I fibrinogen scan technique, phlebography<br><br>PE (until discharge): confirmed by chest roentgenography, lung scan, or pulmonary angiography | |
| Fasting 1985[92] | Intervention (n=52): AES, thigh length Duration: applied the evening before surgery and worn for at least five days until mobile<br><br>Comparison (n=45): UFH, (5000U 2 x daily). Duration: started the evening before surgery for at least 5 days until mobile. All patients received a dose 2-3hrs before surgery | n=97<br><br>People having general surgery (gastro-duodenal 14.4%, large intestine 9.3%, rectal 14.4%, biliary 36.1%, urological 19.6%, other 6.2%) Surgery duration >1hr<br><br>Age (mean, range): intervention, 60 (39-87), comparison, 60 (39-80)<br><br>Male and female (49:48)<br><br>Cancer 31.9%<br><br>Denmark | Major bleeding (time-point not reported): defined as major post-operative haemorrhagic complications<br><br>Fatal PE (time-point not reported): confirmed by autopsy | |
| Fricker 1988[102] | Intervention (n=40): LMWH, standard dose (dalteparin, 2500U, 2 x daily). Duration: started 2 hours before surgery and 12 hours after first administration, followed by LWMH, standard dose (dalteparin 5000U, 1 x | n=80<br><br>People having surgery of a malignant tumour of the abdomen or pelvis Duration >30 minutes<br><br>Age >40 years Males and females (8:72) | DVT (10 days): confirmed by I-fibrinogen uptake test and venography<br><br>PE (up to 8 weeks): confirmed by lung scintigraphy and arterial gazometry | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | daily) for 10 days<br><br>Comparison (n=40):<br>UFH (5000U, 3 x daily).<br>Duration: started 2 hours before surgery, for 10 days | Cancer 100%<br><br>France | Major bleeding (4 weeks): defined as severe postoperative bleeding requiring withdrawal of treatment | |
| Gallus 1973[110] | Intervention (n=108):<br>UFH (5000U, 3 x daily)<br>Duration: started 2 hours before surgery until ambulant<br><br>Comparison (n=118):<br>No VTE prophylaxis | n=226<br><br>People having general surgery (cholecystectomy 37.6%, gastric surgery 16.8%, large bowel surgery 15%, laparotomy 4%, pancreatic surgery 1.3%, abdominal aneurysm 1.3%, hernia repair 5.8%, thoracotomy 4%, laminectomy 6.6%, hip replacement 7.5%)*<br><br>Cancer = 15.5%<br><br>Age >40 years<br>Males and Females (92:134)<br><br>Canada<br><br>*Data on emergency hip surgery and medical patients has been excluded | DVT (mean 8.5-9.8 days): confirmed by I-fibrinogen scanning and venography | |
| Gallus 1976[109] | Intervention (n=408):<br>UFH (5000U, 3 x daily)<br>Duration: started 2 hours before surgery, for 7 days or until discharge<br><br>Comparison (n=412):<br>No VTE prophylaxis | n=820<br><br>People having major abdominothoracic surgery (gallbladder 47.9%, stomach 12.8%, large bowel 11%, other intraabdominal 6%, hernia 9.8%, chest 4.8%. spine 9.1%)<br>Duration of surgery (mean, range) 92, 18-310 minutes<br><br>Age >40 years<br><br>Cancer 17% | DVT (mean 8.4-9.1 days): confirmed by I-labelled fibrinogen scanning, and phlebography | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | Canada | | |
| Gao 2012[111] | Intervention (n=52):<br>• AES, length undefined circumference<br>• IPCD, thigh length<br>Duration: AES was applied pre-operatively and IPCD was applied intra and postoperatively until ambulant<br><br>Comparison (n=56):<br>AES, length undefined<br>Duration: applied pre-operatively until ambulant | n=108<br><br>People gynaecological pelvic surgery (laparotomy 25%, laparoscopic surgery 55.6%, vaginal surgery 19.4%)<br><br>Age >60 years<br>Female<br><br>Cancer 64.8%<br><br>China | DVT (time-point not reported): confirmed by Doppler ultrasound<br><br>PE (time-point not reported): confirmed by pulmonary angiography | |
| Gonzalez 1996[118] | Intervention (n=84):<br>LMWH, standard dose (bemiparin, 2500U, 1 x daily).<br>Duration: started 2 hours before surgery for 7 days<br><br>Comparison (n=82):<br>UFH (5000U, 2 x daily).<br>Duration: started 2 hours before surgery for 7 days | n=166<br><br>People having abdominal surgery (cholecystectomy 52.6%, herniotomy 20.5%, pilorotomy 5.2%, other 21.8%)<br>Duration >30 minutes<br><br>Age >40 years<br>Males and females (65:101)<br><br>Spain | All-cause mortality (8 days)<br><br>DVT (8 days): confirmed by Doppler and plethysmography<br><br>PE (8 days): confirmed by perfusion/ventilation lung scanning and angiography<br><br>Major bleeding (8 days): defined as needing a transfusion of 2 or more units of whole blood, haemoglobin less than 2 g/l, central bleeding and reoperation because of bleeding | |
| Gordon-Smith 1972[120] | Intervention (n=48):<br>UFH (5000U), injected subcutaneously every 12 hours. Duration: started one hour before surgery, for 5 days (a total of 10 | n=98<br><br>People having general surgery (abdominal 87.8%, prostatectomy 4.1%, nephrectomy/ ureterolithotomy 4.1%, | DVT (time-point not reported): confirmed by I-fibrinogen method<br><br>PE (time-point not reported): | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | doses)<br><br>Comparison (n=50):<br>No VTE prophylaxis | radical mastectomy 4.1%)<br><br>Age >40 years<br>Male and female (49:49)<br><br>Cancer 32.7%<br><br>UK | confirmed by phlebography | |
| Hartl 1990[136] | Intervention (n=126):<br>LMWH, low dose (dalteparin, 2500U, 1 x daily)<br>Duration: started 2 hours before operations for at least 7 days post op and fully ambulant<br><br>Comparison (n=124):<br>UFH (5000U, 2 x daily)<br>Duration: started 2 hours before operations for at least 7 days post op and fully ambulant | n=250<br><br>People having abdominal surgery<br>Duration of surgery (mean): intervention 91.7, comparison 106.4 minutes<br><br>Aged >40 years<br>Males and females (144:106)<br><br>Cancer 29.6%<br><br>Austria | All-cause mortality (time-point not reported): confirmed by autopsy<br><br>DVT (time-point not reported): confirmed by fibrinogen uptake test and venography<br><br>Major bleeding (time-point not reported): defined as bleeding requiring transfusion >2 units of blood<br><br>Fatal PE (time-point not reported): confirmed by autopsy | |
| Hata 2016[137] | Intervention (n=152):<br>• UFH (5000U)<br>• Fondaparinux (2.5mg, 1 x daily)<br>• Mechanical thromboprophylaxis (AES + IPCD)<br>UFH started 6 hours after wound closure and continued every 12 hours until the day after surgery. Fondaparinux started on postoperative day 2 until day 5. Mechanical thromboprophylaxis used until full ambulatory | n=298<br><br>People with urological malignancy<br>Duration of surgery >45 minutes<br><br>Age >40 years<br><br>Males and females 282:16<br><br>Japan | PE (time-point not reported): method of confirmation not reported<br><br>Major bleeding (time-point not reported): defined as fatal bleeding, bleeding at vital organs, bleeding or hematoma around the surgical beds necessitating reoperation, or bleeding necessitating transfusion of >400mL red blood | If eGFR ranged from 30-50 mL/min/1.73$^2$ and the risk of bleeding was high, prophylaxis could be reduced to 1.5mg (fondaparinux) or 2000U daily (enoxaparin), at the discretion of the physician |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
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| | Comparison (n=146):<br>• UFH (5000U)<br>• LMWH, standard dose (enoxaparin, 2000U, 2 x daily)<br>• Mechanical thromboprophylaxis (AES + IPCD)<br>UFH started 6 hours after wound closure and continued every 12 hours until the day after surgery. LMWH started on postoperative day 2 until day 5. Mechanical thromboprophylaxis used until full ambulatory | | cells prepared form whole blood, or >2g/dL decrease in haemoglobin level within 48 hours after bleeding onset | |
| Hauch 1988[138] | Intervention (n=20):<br>LMWH, standard dose (tinzaparin, 3500U, 1 x daily).<br>Duration: started 2 hours before operation, until postoperative day 7 or discharge<br><br>Comparison (n=22):<br>LMWH, low dose, (tinzaparin, 2500U, 1 x daily).<br>Duration: started 2 hours before operation, until postoperative day 7 or discharge | n=42<br><br>People having major abdominal surgery (biliary tract surgery 17.1%, gastric surgery 14.3%, colorectal surgery 48.6%, other 20%)<br>Duration of surgery >1 hour<br><br>Age >40 years<br>Male and female (13:22)<br><br>Denmark | DVT (7 days): confirmed by venography<br><br>PE, symptomatic (1 month): method of confirmation not reported<br><br>Major bleeding (1 month): defined as major bleeding complications<br><br>Fatal PE (1 month): confirmed by autopsy | |
| Holford 1976[143] | Intervention (n=48):<br>AES, above knee<br>Duration: applied 12 hours before operation until fully ambulant (4 or 5 days post op)<br><br>Comparison (47):<br>No VTE prophylaxis (control group, no further details reported) | n=95<br><br>People having major surgery (abdominal, pelvic, abdominal and pelvic or thoracic 9.5%)<br><br>Age >40 years<br><br>Cancer 20.4%<br><br>UK | All-cause mortality (time-point not reported)<br><br>DVT (time-point not reported): confirmed by I-fibrinogen test<br><br>PE (time-point not reported): confirmed by lung | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | scanning | |
| Kaaja 1992[156] | Intervention (n=37): LMWH, low dose (enoxaparin, 20mg, 1 x daily). Duration: started 2 hours before surgery for 3 days<br><br>Comparison (n=31): UFH, 5000U, 2 x daily). Duration: started 2 hours before surgery for 3 days | n=68<br><br>People having abdominal hysterectomy<br><br>Age >35 years<br>Female<br><br>Cancer 25%<br><br>Finland | PE (3-4 weeks): confirmed by lung scanning<br><br>Major bleeding (time-point not reported): defined as bleeding necessitating reoperation and/or blood transfusion, and cessation of heparin administration | |
| Kakkar 1972[160] | Intervention (n=39): UFH (5000U, 2 x daily) Duration: started 2 hours before surgery for 7 days<br><br>Comparison (n=39): No VTE prophylaxis | n=78<br><br>People having major surgery (gastric 24.4%, colonic 16.7%, biliary, 33.3% thoracic 5.1%, urological 16.7%, laparotomy 3.8%)<br><br>Age >40 years<br>Male and female (45:33)<br><br>United States | DVT (10 days): confirmed by I-labelled fibrinogen test<br><br>PE (time-point not reported): method of confirmation not reported | |
| Kakkar 1993[159] | Intervention (n=1894): LMWH, low dose (dalteparin, 2500U, 1 x daily) Duration: started 1-4 hours before operation, for at least 5 days and until fully mobile<br><br>Comparison (n=1915): UFH (5000U), 2 x daily Duration: started 1-4 hours before operation, for at least 5 days and until fully mobile | n=3809<br><br>People having major abdominal surgery (colectomy 23.4%, abdominoperineal resection 4.5%, cholecystectomy 25%, other biliary procedures 1.3%, laparotomy 3.9%, gynaecological procedure 25.4%, oesophageal procedure 2.8%, gastric procedure 6.6%, urological procedure 2.7%, other 3.6%) Duration >30 minutes<br><br>Age > 40 years<br>Male and female (1314:2495) | All-cause mortality (4-8 weeks)<br><br>PE (4-8 weeks): confirmed by ventilation/perfusion scanning or pulmonary angiography<br><br>Major bleeding (4-8 weeks) defined as: blood loss during the perioperative period that required discontinuation of prophylaxis, when bleeding was clearly attributable to the trial drug, when bleeding | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | Cancer 36.9%<br><br>UK | required reoperation to control it, or when a wound haematoma developed whether or not it required evacuation.<br><br>Fatal PE (4-8 weeks): confirmed by autopsy | |
| Kakkar 2010[158] | Intervention (n=315): extended duration LMWH, high dose (bemiparin, 3500U, 1 x daily)<br>Duration: before randomisation, all patients received LMWH for 8±2 days, starting 6 hours after surgery. Patients then received LMWH for 20 ±2 additional days<br><br>Comparison (n=310): standard duration LMWH, high dose (bemiparin, 3500U) + placebo (0.9% sodium chloride 0.2mL).<br>Duration: before randomisation, all patients received LMWH for 8±2 days, starting 6 hours after surgery. Patients then received placebo for 20±2 additional days | n=625<br><br>People having abdominal or pelvic surgery for cancer (gastrointestinal tract (colorectal, gastric and other) 80.6%, urologic 7.5%, female reproductive organs 11.4%, retroperitoneal 0.5% )<br>Duration >30 minutes<br><br>Age >40 years<br>Males and females (330:295)<br><br>34 centres in 3 countries (UK, Spain, Italy) | All-cause mortality (90 days)<br><br>DVT (28 days): confirmed by venography or Doppler ultrasound<br><br>PE (28 days): confirmed by perfusion/ventilation lung scintigraphy, pulmonary arteriography or spiral computed tomography<br><br>Major bleeding (22 days): defined as fatal bleeding, clinically overt bleeding, bleeding leading to a transfusion of 2 or more units of packed cells or whole blood, retroperitoneal or intracranial bleeding, or clinically overt bleeding warranting treatment cessation | |
| Koller 1986A[170] | Intervention (n=23): LMWH, high dose (dalteparin, 7500U, 1 x daily)<br>Duration: started one hour before operation, | n=43<br><br>People having general surgery (herniotomy 51.2%, cholecystectomy 18.6% , breast operation | All-cause mortality (time-point not reported)<br><br>DVT (30 days): confirmed by | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | for a minimum of 5 days<br><br>Comparison (n=20):<br>UFH (5000U), 2 x daily<br>Duration: started one hour before operation, for a minimum of 5 days | 9.3%, vagotomy 4.7%, colon resection 9.3%, lung resection 2.3%, other 4.7%)<br><br>Age >20 years<br>Males and females (28:15)<br><br>Switzerland | fibrinogen uptake test and venography<br><br>Major bleeding (time-point not reported): defined as bleeding requiring discontinuation of prophylaxis | |
| Koller 1986B[170] | Intervention (n=74):<br>LMWH, low dose (dalteparin, 2500U, 1 x daily)<br>Duration: started one hour before operation, for at least 5 days<br><br>Comparison (n=72):<br>UFH (5000U), 2 x daily<br>Duration: started one hour before operation, for at least 5 days | n=146<br><br>People having general surgery (herniotomy 60.3%, cholecystectomy 17.8%, prox. selective vagotomy 2.1%, colon resection 5.5%, breast operation 9.6%, other 4.5%)<br><br>Age >20 and <80<br>Males and females (89:57)<br><br>Cancer 14.4%<br><br>Switzerland | All-cause mortality (time-point not reported)<br><br>DVT (30 days): confirmed by fibrinogen uptake test and venography<br><br>PE (30 days): confirmed by pulmonary perfusion/ventilation scans<br><br>Major bleeding (time-point not reported): defined as bleeding complications leading to discontinuation of prophylaxis, and transfusion >2 units of blood | |
| Lahnborg 1975[175,176] | Intervention (n=58):<br>UFH (5000U, 2 x daily)<br>Duration: started 2-5 hours before surgery, for 5 days<br><br>Comparison (n=54):<br>No VTE prophylaxis | n=112<br><br>People having major abdominal surgery<br><br>Age >40 years<br><br>Sweden<br><br>No further details reported | All-cause mortality (5 days)<br><br>PE (time-point not reported): confirmed by pulmonary photo scanning<br><br>Major bleeding (time-point not reported): not defined | |
| Liezorovicz 1991[193] | Intervention 1 (n=431):<br>LMWH, low dose (tinzaparin, 2500U, 1 x | n=1290 | All-cause mortality (1 month) | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | daily)<br>Duration: started 2 hours before operation, for at least 7 days and maximum of 10 days<br><br>Intervention 2 (n=430):<br>LMWH, standard dose (tinzaparin, 3500U, 1 x daily)<br>Duration: started 2 hours before operation, for at least 7 days and maximum of 10 days<br><br>Comparison (n=429):<br>UFH (5000U), 2 x daily<br>Duration: started 2 hours before operation, for at least 7 days and maximum of 10 days | People having general surgery (abdominal 71.4%, gynaecological 13.5%, urological 9.8% or thoracic 5.3%)<br>Duration > 30minutes<br><br>Age >40 years<br>Male and female (513:777)<br><br>Cancer 38.5%<br><br>France and UK | DVT (8 days): confirmed by fibrinogen uptake test and venography<br><br>PE (1 month): confirmed by angiography<br><br>Major bleeding (discharge – 1 month): defined as haemorrhage needing transfusion and/or reintervention and/or treatment discontinuation | |
| Marassi 1993 [202] | Intervention (n=31):<br>LMWH, high dose (nadroparin, 3825U, 1 x daily).<br>Duration: started 2 hours before operation, for 7 days<br><br>Comparison (n=33):<br>No VTE prophylaxis | n=64<br><br>People having cancer-related abdominal surgery<br><br>Age > 40 years<br>Males and females (36:25)<br><br>Cancer surgery 100%<br><br>Italy | DVT (7 days): confirmed by FUT and venography | |
| Maxwell 2001[204] | Intervention (n=106):<br>IPCD, length not reported.<br>Duration: applied at induction of anaesthesia and continued for first 5 days postoperatively. Device stopped when patient was walking and restarted when back in bed.<br><br>Comparison (n=105):<br>LMWH, standard dose, (dalteparin, 5000U, 1 x | n=228<br><br>People having gynaecological surgery (duration, median: intervention 199 minutes, comparison 197 minutes)<br><br>Age >40 years<br>Females<br><br>Cancer 74.9%<br><br>United states | DVT (30 days): confirmed by real-time US compression technique with duplex and colour Doppler imaging<br><br>PE (30 days): method of confirmation not reported<br><br>Thrombocytopaenia (time-point not reported) | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | daily).<br>Duration: 2500U given 1-2 hours before surgery and 12 hours after first dose. Then from postoperative day 1, 5000U was administered once daily up to post-operative day 5. If the patient was confined to bed after day 5, continued prophylaxis until day of discharge or ambulatory. | | | |
| McLeod 2001[210] | Intervention (n=674):<br>LMWH, standard dose, (enoxaparin, 40mg, 1 x daily).<br>Duration: started 2 hours before surgery, for 10 days<br><br>Comparison (n=675):<br>UFH, (5000 units, 3 x daily)<br>Duration: started 2 hours before surgery, for 10 days | n=1349<br><br>People having abdominal (colorectal) surgery<br>Duration >1 hour<br><br>Age (mean, SD): intervention 52 (18), control 50 (17)<br><br>Male and female (731:618)<br><br>Cancer 35%<br><br>Canada | PE (10 days): confirmed by lung scan or pulmonary angiogram<br><br>Major bleeding (10 days): defined as intracranial, retroperitoneal, or clinically overt haemorrhage associated with a decrease in the haemoglobin level of more than 20 g/L, the transfusion of 2 or more units of packed cells, or the need for surgical intervention | |
| Nagata 2015[223] | Intervention (n=16):<br>• Foot impulse device (FID)<br>• IPCD, below knee<br>• LMWH, standard dose (enoxaparin, 20mg, 2x daily)<br>Duration: FID was applied immediately before surgery. Post operatively, patients switched to IPCD until after the first LMWH injection on | n=30<br><br>People having major abdominal or pelvic surgery (hysterectomy 53.3%, laparotomy 30%, debulking surgery 10%, tumour sampling 6.7%)<br>Duration >45 minutes<br><br>Age >40 years<br>Females<br><br>100% cancer | DVT (11 days): confirmed by contrast CT<br><br>PE (11 days):confirmed by contrast CT<br><br>Major bleeding (11 days): defined as red blood cell transfusion of more than two units, a decrease in haemoglobin | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | postoperative day 2. LMWH commenced on postoperative day 2 for 7 days<br><br>Comparison (n=14):<br>• FID<br>• IPCD, below knee<br>Duration: FID was applied immediately prior to surgery. Post operatively, patients switched to IPCD until fully ambulated | Japan | concentration of more than 2g/dL, intracranial, intraocular, gastrointestinal, epidural haemorrhage or bleeding from the wounds, the abdomen or retroperitoneal cavity that required surgical treatment<br><br>Thrombosytopenia (6 days) | |
| Nicolaides 1983[232] | Intervention 1 (n=50):<br>• IPCD, full leg<br>• AES, length not reported<br>Duration: IPCD worn during surgery and for 72 hours post-op or until ambulant, then AES applied until discharge<br><br>Intervention 2 (n=50):<br>UFH, (5000U, 2 x daily)<br>Duration: started 2 hours before operation, until discharge<br><br>Comparison (n=50):<br>Electrical calf stimulation at 12 impulses/min.<br>Duration: started after induction of anaesthesia and continued for duration of operation | n=150<br><br>People having abdominal surgery<br>Age >30 years<br><br>Gender not reported<br><br>Cancer 37.3%<br><br>UK | DVT (until discharge): confirmed by 125I FUT | |
| Nurmoha med 1995[235] | Intervention (n=718):<br>LMWH, low dose (enoxaparin, 20mg 1 x daily)<br>Duration: started 2 hours before operation, for 10 days or until discharge<br><br>Comparison (n=709): | n=1427<br><br>People having general surgery (gastric 12.5%, cholecystectomy 23%, other biliary 2.4%, colon/rectum 28.9%, herniotomy 6%, hysterectomy 9.8%, other gynaecological 3.8%, | All-cause mortality (time point not reported)<br><br>DVT (10 days): confirmed by fibrinogen 1 125 uptake test and unilateral venography | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
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| | UFH (5000U), 3 x daily<br>Duration: started 2 hours before operation, for 10 days or until discharge | urological 8%, other 4.2%)<br>Duration of surgery >45 minutes<br><br>Aged >40 years<br>Males and females (670:734)<br><br>Cancer 35.8%<br><br>20 centres in Belgium, Germany, The Netherlands, Spain, UK, and New Zealand | PE (time point not reported): clinical suspicion or autopsy<br><br>Major bleeding (time point not reported): defined as clinically overt with either a fall of haemoglobin of 20g/L or when it led to a transfusion of 2 or more units of packed cells, or if it was retroperitoneal or intracranial<br><br>Fatal PE (time-point not reported): confirmed by autopsy | |
| Ockelford 1989 [236] | Intervention (n=102):<br>LMWH low dose, (dalteparin, 2500U, 1 x daily).<br>Duration: started 1-2 hours before operation, for 5-9 days<br><br>Comparison (n=95):<br>No VTE prophylaxis (placebo) | n=197<br><br>People having abdominal surgery<br>Duration >30 minutes<br><br>Age >40 years<br>Males and females<br><br>Cancer surgery 43%<br><br>New Zealand | All-cause mortality (42 days)<br><br>DVT (42 days): confirmed by FUT<br><br>PE (42 days): not reported<br><br>Major bleeding (42 days): defined as when treatment discontinued because of excess bleeding<br><br>Thrombocytopaenia (42 days): not reported | |
| Onarheim 1986[238] | Intervention (n=25):<br>LMWH, standard dose (dalteparin, 5000U, 1 x daily).<br>Duration: started 2 hours before surgery, for 6 days<br><br>Comparison (n=27):<br>UFH 5000U, 2 x daily | n=52<br><br>People having major abdominal surgery for gastric, colonic, or rectal malignancy<br><br>Age >40 years<br><br>Cancer 100% | All-cause mortality (30 days)<br><br>DVT (30 days): confirmed by fibrinogen uptake test and phlebography<br><br>PE (30 days): | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Duration: started 2 hours before surgery, for 6 days | Norway | method of confirmation not reported<br><br>Major bleeding (30 days): defined as bleeding requiring reoperation or interruption of prophylaxis | |
| Osman 2007[239] | Intervention 1 (n=25): LMWH, standard dose, (tinzaparin, 3500U, 1 x daily)<br>Duration: for 1 week post operatively. No further details reported<br><br>Intervention 2 (n=25): UFH, (5000U), 2 x daily<br>Duration: for 1 week post operatively. No further details reported<br><br>Comparison (n=25):<br>No VTE prophylaxis | n=75<br>People having live-donor renal transplantation<br>Duration not reported<br><br>Age >16 years<br>Male and female (52:23)<br><br>Egypt | DVT (2 weeks): radiologically, ultrasonography, CT or MRI and isotope renography were used to diagnose postoperative complications<br><br>PE (2 weeks): radiologically, ultrasonography, CT or MRI and isotope renography were used to diagnose postoperative complications<br><br>Major bleeding (2 weeks): defined as massive haemorrhage necessitating exploration | |
| Porteous 1989[245] | Intervention (n=56): AES, above knee.<br>Duration: worn until discharge. No further details reported<br><br>Comparison (n=58): AES, below knee.<br>Duration: worn until discharge. No further details reported | n=124<br><br>People having major abdominal surgery<br>Duration of surgery (mean, SD): intervention 110 (39), comparison 115 (44)<br><br>Age >40 years<br>Males and females (49:65)<br><br>Malignant disease 40.4%<br><br>UK | DVT (time-point not reported): confirmed by I-labelled fibrinogen uptake test and phlebography | |
| Rasmussen | Intervention (n=205): | n=427 | All-cause mortality | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
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| 2006[251] | • LMWH, standard dose, extended duration (dalteparin, 5000 U, 1 x daily).<br>• AES, length not reported<br>Duration: LMWH started the day before surgery, for 28 days. AES worn for 7 days<br><br><u>Comparison (n=222):</u><br>• LMWH, standard dose, standard duration (dalteparin, 5000 U, 1 x daily)<br>• AES length not reported<br>Duration: LMWH started the day before surgery, for 7 days. AES worn for 7 days | People having major abdominal surgery<br>Duration > 1 hour<br><br>Age >18 years<br>Male and female (174:169)<br><br>Denmark and Norway | (2 months)<br><br>DVT (day 28): confirmed by bilateral venography<br><br>PE (2 months): confirmed by ventilation/perfusion scanning<br><br>Major bleeding (28 days): defined as bleeding that resulted in death, fall in haemoglobin ≥ 2g/dl, transfusion ≥2 units of blood, retroperitoneal, intracranial, intraocular, resulted in life threatening event, or surgical/medical intervention required to stop it<br><br>Fatal pulmonary embolism (up to 2 months): method of confirmation not reported | |
| Rasmussen 1988[250] | <u>Intervention 1 (n=74):</u><br>AES, knee length<br>Duration: applied the evening before surgery, for at least 5 days<br><br><u>Intervention 2 (n=85):</u><br>UFH (5000U), administered subcutaneously every 12 hours.<br>Duration: started the evening before surgery, for at least 5 days<br><br><u>Comparison (n=89):</u><br>• AES, knee length | n=248<br><br>People having major abdominal surgery (colon+rectum 21%, biliary 30.6%, gastric+pancreas 12%, urologic 14.9%, gynaecologic 14.1%, other 7.3%)<br>Duration >1 hour<br><br>Age >40 years<br>Males and females (109:139)<br><br>Denmark | All-cause mortality (time-point not reported)<br><br>PE (time-point not reported): method of confirmation not reported<br><br>Major bleeding (time-point not reported): defined as major postoperative haemorrhage | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | • UFH (5000U)<br>Duration: as above | | | |
| Sakon 2010[260] | Intervention (n=113):<br>• IPCD, length not reported<br>• LMWH, standard dose (enoxaparin 20mg 2 x daily)<br>Duration: all patients received at least one course of postsurgical IPCD before first LMWH dose. No further details on IPCD. LMWH started 24-36 hours after surgery and continued for 14 days (and for at least 7 consecutive days).<br><br>Comparison (n=38):<br>IPCD length not reported<br>Duration: left to the discretion of the investigator | n=151<br><br>People having a laparotomy for cancer (stomach 42.1%, rectum 14.9%, colon 21.9%, prostate 4.4%, uterus 4.4%, ovary 2.6%, hepatic 2.6%, other 13.2%) *<br>Duration >45 minutes<br><br>Age >40 years<br>Males and females (69:45)<br><br>100% cancer<br><br>Japan<br><br>*total is more than 100% as some patients had surgery at multiple sites | DVT (14 days): confirmed by ultrasonography and venography<br><br>PE (14 days): confirmed by ventilation/perfusion lung scan, pulmonary angiography or computerised tomography<br><br>Major bleeding (14 days): defined as the event resulted in death, was clinically overt, was retroperitoneal, intracranial, or intraocular, or resulted in serious or life threatening clinical events, or required surgical or medical intervention to control the event | |
| Scurr 1981[268] | Intervention (n=33):<br>foot pump.<br>Duration: applied from the beginning of the procedure until the patient regained consciousness<br><br>Comparison (n=33):<br>No VTE prophylaxis | n=66<br><br>People having major abdominal surgery<br>Duration >20 minutes<br><br>Age >40 years<br><br>Cancer 77%<br><br>UK | All-cause mortality (7 days)<br><br>DVT (7 days): confirmed by fibrinogen scanning | |
| Soderdahl 1997[272] | Intervention (n=47):<br>IPCD, thigh-length.<br><br>Comparison (n=43):<br>IPCD, calf-length<br><br>Duration: begun pre-anaesthetic and continued until patient fully ambulatory or | n=90<br><br>People having abdominal (urological) surgery (duration not reported)<br><br>Age (mean, range): intervention 64.8 (46-90), comparison 58.6 (24-77) | DVT (3 months): confirmed by bilateral duplex ultrasound<br><br>PE (3 months): confirmed by ventilation perfusion scan and pulmonary | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | until discharge | Male and female<br><br>United States | angiography<br><br>Fatal PE (3 months): method of confirmation not reported | |
| Song 2014[273] | Intervention (n=108):<br>• LMWH, standard dose (enoxaparin 40mg, 1 x daily)<br>• IPCD, length not reported<br>Duration: LMWH started post-operatively until discharge, IPCD applied pre-operatively until discharge<br><br>Comparison (n=112):<br>IPCD, length not reported<br>Duration: applied pre-operatively until discharge | n=220<br><br>People with cancer having gastrectomy (100% adenocarcinoma)<br><br>Age >20 years<br>Male to female (150:70)<br><br>Cancer 100%<br><br>South Korea | DVT (4 days): confirmed by duplex ultrasonography<br><br>PE (30 days): 'detected'<br><br>Major bleeding (30 days): definition not reported | |
| Strand 1975[284] | Intervention (n=50):<br>UFH (5000U, 2 x daily)<br>Duration: started 1-3 hours before surgery or on admission, for 7 days<br><br>Comparison (n=50):<br>No VTE prophylaxis (placebo) | n=100<br><br>People having gastrointestinal or urinary tract surgery (stomach 16.7%, small intestine 2.9%, biliary 21.6%, colon 21.6%, rectum 4.9%, urinary 27.4%, other 6.9%)<br><br>Age >30 years<br>Males and females (49:51)<br><br>Cancer 28%<br><br>Denmark | DVT (10 weeks): confirmed by I fibrinogen method<br><br>PE (10 weeks): method of confirmation not reported<br><br>Fatal PE (10 weeks): confirmed by autopsy | |
| Taberner 1978[286] | Intervention 1 (n=49):<br>UFH (5000U, 2 x daily)<br>Duration: started 2 hours before surgery on, for 7 days<br><br>Intervention 2 (n=48):<br>VKA (acenocoumarol), 6mg | n=145<br><br>People having abdominal or vaginal surgery (hysterectomy or laparotomy 58.6%, pelvic floor repair 41.4.2%)<br><br>Age >40 years | DVT (7 days): confirmed by fibrinogen scan | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Duration: started at least 5 days before surgery<br><br>Comparison (n=48):<br>No VTE prophylaxis (placebo) | Cancer 5.5%<br><br>UK | | |
| Torngren 1978[290,291] | Intervention (n=63):<br>UFH (5000U, 2 x daily)<br>Duration: started 2 hours before surgery or on admission, for 6-8 days<br><br>Comparison (n=61):<br>No VTE prophylaxis | n=124<br><br>People having abdominal surgery<br>Duration of surgery >20 minutes<br><br>Age >40 years<br>Males and females (66:58)<br><br>Cancer 24%<br><br>Sweden | All-cause mortality (6-8 days): confirmed by autopsy<br><br>DVT (up to 14 days): confirmed by I-fibrinogen test<br><br>PE (6-8 days): confirmed by autopsy<br><br>Major bleeding (6-8 days): defined at bleeding requiring a transfusion<br><br>Fatal PE (6-8 days): confirmed by autopsy | |
| Tsapogas 1971 [292] | Intervention (n=51):<br>AES, below knee.<br>Duration: day of surgery until discharge<br><br>Comparison (n=44):<br>No VTE prophylaxis | n=95<br><br>People having major abdominal surgery<br><br>Age >40 years<br>Male and female (93:2)<br><br>USA | DVT (7 days): confirmed by fibrinogen uptake test and phlebography | |
| Turner 1984 [293] | Intervention (n=104):<br>AES, above knee<br>Duration: started on day of admission, discontinuation point not reported<br><br>Comparison (n=92):<br>No VTE prophylaxis | n=196<br><br>People having elective gynaecological surgery<br><br>Age >35 years<br>Female<br><br>UK | DVT (time-point not reported): confirmed by Fibrinogen Uptake Test<br><br>PE (time-point not reported): method of confirmation not reported | |
| Turpie | Intervention (n=650): | n=1309 | All-cause mortality | The use of AES was left to the |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| 2007[294] | • Fondaparinux (2.5mg, 1 x daily)<br>• IPCD, mixed length<br>Duration: started 6-8 hours after surgery, provided that haemostasis was achieved, or 2 hours after removal of intrathecal or epidural catheter. Second injection given 16-28 h after 1st injection. Duration was 5-9 days. IPCD duration was left to the investigators discretion<br><br><u>Comparison (n=659):</u><br>IPCD, mixed length<br>Duration: left to the investigators discretion | People having abdominal surgery<br>Duration >45 minutes<br><br>Age > 40 years<br><br>Male and female (635:650)<br><br>United States | (32 days)<br><br>DVT (days 5-10): confirmed by bilateral ascending contrast venography<br><br>PE, symptomatic (32 days): confirmed by a high-probability lung scan, non-high probability lung scan defect plus confirmed DVT, pulmonary angiography, helical computed tomography, or autopsy)<br><br>Major bleeding (day 32): defined as bleeding that was fatal, retroperitoneal, intracranial, or involved any other critical organ, led to intervention, or was associated with a bleeding index of 2.0 or more.<br><br>Fatal PE (32 days): confirmed by: autopsy | investigator's discretion |
| Van Vroonhoven 1974[302] | <u>Intervention (n=50):</u><br>UFH (dose not reported, 2x daily).<br>Duration: begun 2 hours before operation, for 8 days<br><br><u>Comparison (n=50):</u><br>VKA (acenocoumarol, PTT 5-10% of normal).<br>Duration: Begun on evening of day of op, or 1st post-op day. Continued for 7 days | n=100<br><br>People having general surgery (gastric 24%, biliary 28%, colonic 15%, herniotomy 16%, abdominal wall 6%, laparotomy 6%, other 5%)<br><br>Age >40 years<br><br>Cancer 18%<br><br>Netherlands | DVT (time-point not reported): confirmed by I-fibrinogen test<br><br>Major bleeding (time-point not reported): defined as overt bleeding complications | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Vandendris 1980 [303] | Intervention (n=31):<br>UFH (5000U, 3 x daily)<br>Duration: started 2 hours before operation for 6 days<br><br>Comparison (n=33):<br>No VTE prophylaxis (placebo, 0.2 ml distilled water) | n=64<br><br>People having urologic surgery<br><br>Age (mean): intervention 72.2, comparison 70<br><br>Belgium | DVT (time-point not reported): confirmed by I-labelled fibrinogen test and clinical examination<br><br>PE (time-point not reported): confirmed by clinical examination | Patients with varicose veins wore AES during and after the operation |
| Wille-Jorgensen 1985 [317] | Intervention (n=94):<br>• AES, thigh length<br>• UFH (5000U 2 x daily)<br>Duration: AES applied before surgery during the observation period. UFH administered 1 hour preoperatively for 7 days or until discharge<br><br>Comparison (n=102):<br>UFH (5000U, 2 x daily).<br>Duration: administered 1 hour preoperatively for 7 days or until discharge | n=196<br><br>People having abdominal surgery<br>Duration >45 minutes<br><br>Age >39 years<br>Male and female (105:71)<br><br>Denmark | DVT (7 days): confirmed by Fibrinogen Uptake Test, and phlebography and perfusion lung scan if Fibrinogen Uptake Test was positive<br><br>PE (30 days): confirmed by scintigraphy or autopsy<br><br>Fatal PE (30 days): confirmed by scintigraphy | |
| Wille-Jorgensen 1991 [316] | Intervention (n=94):<br>• AES, above knee<br>• UFH (5000U 2 x daily)<br>Duration: AES applied preoperatively and worn until full mobilisation. UFH administered on day of surgery for 7 days or until discharge.<br><br>Comparison (n=84):<br>UFH (5000U 2 x daily)<br>Duration: administered on day of surgery for 7 | n=178<br><br>People having abdominal surgery<br>Duration >1 hour<br><br>Age >39 years<br>Male and female (58:102)<br><br>Denmark | All-cause mortality (30 days)<br><br>DVT (30 days): confirmed by I-fibrinogen uptake test and phlebography<br><br>PE (30 days): confirmed by perfusion pulmonary scintigram and roentgenogram | |

| Included studies | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | days or until discharge | | | |

**Table 169: 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 Control | Risk difference with AES (above knee) versus no VTE prophylaxis (95% CI) |
| All-cause mortality | 291 (2 studies) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 16 fewer to 16 more)[d] |
| DVT | 291 (2 studies) time-point not reported | MODERATE[a] due to risk of bias | RR 0.41 (0.23 to 0.73) | 194 per 1000 | 115 fewer per 1000 (from 52 fewer to 150 fewer) |
| PE | 291 (2 studies) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.13 (0 to 6.68) | 7 per 1000 | 6 fewer per 1000 (from 7 fewer to 39 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 170: Clinical evidence summary: AES (below 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 Control | Risk difference with AES (below knee) versus no VTE prophylaxis (95% CI) |
| DVT | 95 (1 study) 7 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.29 (0.06 to 1.35) | 136 per 1000 | 97 fewer per 1000 (from 128 fewer to 48 more) |

| 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 AES (below knee) versus no VTE prophylaxis (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

**Table 171: Clinical evidence summary: AES (undefined) versus no 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 AES (undefined) versus no VTE prophylaxis (95% CI) |
| DVT | 200<br>(1 study)<br>7 days | MODERATE[a]<br>due to risk of bias | RR 0.43<br>(0.25 to 0.73) | 359 per 1000 | 205 fewer per 1000<br>(from 97 fewer to 269 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

**Table 172: Clinical evidence summary: AES (above knee) versus UFH**

| 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 AES (above knee) versus UFH (95% CI) |
| Fatal PE | 97<br>(1 study)<br>time-point not reported | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.12<br>(0 to 5.9) | 22 per 1000 | 20 fewer per 1000<br>(from 22 fewer to 96 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 173: Clinical evidence summary: AES (below knee) versus UFH**

| 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 AES (below knee) versus UFH (95% CI) |
| All-cause mortality | 159 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 24 fewer to 24 more)[e] |
| PE | 159 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 24 fewer to 24 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 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 Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

**Table 174: Clinical evidence summary: AES (above knee) versus AES (below knee)**

| 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 AES above knee versus AES below knee (95% CI) |
| DVT | 114 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | RR 3.11 (0.33 to 28.99) | 17 per 1000 | 36 more per 1000 (from 12 fewer to 483 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 175: Clinical evidence summary: AES (below knee) + UFH versus AES (below knee)**

| 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 AES + UFH (95% CI) |
| All-cause mortality | 163 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 24 fewer to 24 more)[e] |
| PE | 163 (1 study) time-point not reported | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 24 fewer to 24 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 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 Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

**Table 176: Clinical evidence summary: AES (above knee) + UFH versus UFH**

| 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 AES (above knee) + UFH versus UFH (95% CI) |
| All-cause mortality | 160 (1 study) up to 30 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.49 (0.74 to 3.01) | 136 per 1000 | 67 more per 1000 (from 35 fewer to 273 more) |
| DVT | 336 (2 studies) up to 30 days | MODERATE[a] due to risk of bias | RR 0.16 (0.05 to 0.54) | 111 per 1000 | 93 fewer per 1000 (from 51 fewer to 106 fewer) |
| PE | 336 | | RR 0.35 | 34 per 1000 | 23 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 AES (above knee) + UFH versus UFH (95% CI) |
| | (2 studies)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | (0.07 to 1.68) | | (from 33 fewer to 24 more) |
| Fatal PE | 176<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.14<br>(0 to 7.14) | 11 per 1000 | 10 fewer per 1000<br>(from 11 fewer to 63 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 177: Clinical evidence summary: AES (below knee) + UFH versus UFH**

| 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 AES (below knee) + UFH versus UFH (95% CI) |
| All-cause mortality | 174<br>(1 study)<br>time-point not reported | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 22 fewer to 22 more)[e] |
| PE | 174<br>(1 study)<br>time-point not reported | VERY LOW[a,b,c]<br>due to risk of bias, imprecision, indirectness | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 22 fewer to 22 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

| 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 AES (below knee) + UFH versus UFH (95% CI) |
| e Risk difference calculated in Review Manager | | | | | |

**Table 178: Clinical evidence summary: AES (above knee) + IPCD (full leg) versus AES (above knee)**

| 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 AES (above knee) + IPCD versus AES (95% CI) |
| DVT | 77 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.21 (0.03 to 1.68) | 128 per 1000 | 101 fewer per 1000 (from 124 fewer to 87 more) |
| PE | 77 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.03 (0.07 to 15.82) | 26 per 1000 | 1 more per 1000 (from 24 fewer to 380 more) |
| Fatal PE | 77 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.14 (0 to 7) | 26 per 1000 | 22 fewer per 1000 (from 26 fewer to 130 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<br>b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs | | | | | |

**Table 179: Clinical evidence summary: AES (undefined) + IPCD (full leg) versus AES (undefined)**

| 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 AES (undefined) + IPCD versus AES (95% CI) |
| DVT | 108 | | RR 0.38 | 250 per 1000 | 155 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 AES (undefined) + IPCD versus AES (95% CI) |
| | (1 study) time-point not reported | LOW[a,b] due to risk of bias, imprecision | (0.15 to 0.99) | | (from 2 fewer to 213 fewer) |
| PE | 108 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.08 (0.07 to 16.78) | 18 per 1000 | 1 more per 1000 (from 17 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

**Table 180: Clinical evidence summary: AES (undefined) + IPCD (full leg) versus UFH**

| 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 AES + IPCD versus UFH (95% CI) |
| DVT | 100 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.43 (0.12 to 1.56) | 140 per 1000 | 80 fewer per 1000 (from 123 fewer to 78 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 181: Clinical evidence summary: AES (undefined) + IPCD (full leg) versus electrical stimulation**

| 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 AES + IPCD versus electrical stimulation (95% CI) |
| DVT | 100 | | RR 0.25 | 240 per 1000 | 180 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 AES + IPCD versus electrical stimulation (95% CI) |
| | (1 study)<br>time-point not reported | LOW[a,b]<br>due to risk of bias, imprecision | (0.08 to 0.83) | | (from 41 fewer to 221 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 182: Clinical evidence summary: Electrical stimulation versus UFH**

| 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 Electrical stimulation versus UFH (95% CI) |
| DVT | 100<br>(1 study)<br>time-point not reported | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 1.71<br>(0.74 to 3.99) | 140 per 1000 | 99 more per 1000<br>(from 36 fewer to 419 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 183: Clinical evidence summary: Foot pump versus no 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 Foot pump versus no prophylaxis (95% CI) |
| All-cause mortality | 66<br>(1 study)<br>7 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.14<br>(0 to 6.82) | 30 per 1000 | 26 fewer per 1000<br>(from 30 fewer to 145 more) |

| 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 Foot pump versus no prophylaxis (95% CI) |
| DVT | 66<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.4<br>(0.18 to 0.9) | 455 per 1000 | 273 fewer per 1000<br>(from 45 fewer to 373 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 184: Clinical evidence summary: FID + IPCD (below knee) + LMWH (low dose) versus FID + IPCD (below knee)**

| 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 FID + IPCD + LMWH versus FID + IPCD (95% CI) |
| DVT | 30<br>(1 study)<br>11 days | VERY LOW[a,b,c]<br>due to risk of bias, imprecision, indirectness | RR 0.29<br>(0.03 to 2.5) | 214 per 1000 | 152 fewer per 1000<br>(from 208 fewer to 321 more) |
| PE | 30<br>(1 study)<br>11 days | LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.11<br>(0.01 to 1.13) | 214 per 1000 | 185 fewer per 1000<br>(from 212 fewer to 21 more) |
| Thrombocytopaenia | 30<br>(1 study)<br>6 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 121 fewer to 121 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 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

| 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 FID + IPCD + LMWH versus FID + IPCD (95% CI) |
| d Could not be calculated as there were no events in the intervention or comparison group<br>e Risk difference calculated in Review Manager | | | | | |

**Table 185: Clinical evidence summary: IPCD (below 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 Control | Risk difference with IPCD versus no prophylaxis (95% CI) |
| All-cause mortality | 107<br>(1 study)<br>42 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 36 fewer to 36 more)[e] |
| DVT | 473<br>(4 studies)<br>up to 90 days | VERY LOW[a,b,c]<br>due to risk of bias, inconsistency, imprecision | RR 0.64<br>(0.26 to 1.59) | 165 per 1000 | 59 fewer per 1000<br>(from 122 fewer to 97 more) |
| PE | 354<br>(3 studies)<br>42 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 2.19<br>(0.58 to 8.24) | 17 per 1000 | 21 more per 1000<br>(from 7 fewer to 126 more) |
| Fatal PE | 313<br>(2 studies)<br>up to 90 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.5<br>(0.05 to 4.81) | 13 per 1000 | 6 fewer per 1000<br>(from 12 fewer to 47 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<br>b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs<br>c Downgraded by 1 increment because heterogeneity, $1^2$=67%, p=0.03, unexplained by subgroup analysis.<br>d Could not be calculated as there were no events in the intervention or comparison group<br>e Risk difference calculated in Review Manager | | | | | |

**Table 186: Clinical evidence summary: IPCD (full leg) versus IPCD (below knee)**

| 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 IPCD full length versus IPCD below knee (95% CI) |
| DVT | 90 (1 study) 90 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.12 (0 to 6.24) | 23 per 1000 | 20 fewer per 1000 (from 23 fewer to 106 more) |
| PE | 90 (1 study) 90 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 6.79 (0.13 to 343.33) | 0 per 1000 | Not estimable[c] |
| Fatal PE | 90 (1 study) 90 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.12 (0 to 6.24) | 23 per 1000 | 20 fewer per 1000 (from 23 fewer to 106 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 comparison group

**Table 187: Clinical evidence summary: IPCD (full leg) versus VKA**

| 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 IPCD versus warfarin (95% CI) |
| All-cause mortality | 100 (1 study) 7-14 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 38 fewer to 38 more)[e] |
| DVT | 100 (1 study) 7-14 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 8.58 (0.53 to 139.81) | 0 per 1000 | Not estimable[F] |
| PE | 100 (1 study) | VERY LOW[a,b,c] due to risk of bias, imprecision, | Peto OR 8.4 (0.17 to 426.1) | 0 per 1000 | Not estimable[F] |

| 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 IPCD versus warfarin (95% CI) |
| | 7-14 days | indirectness | | | |

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 Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager
f Could not be calculated as there were no events in the comparison group

**Table 188: Clinical evidence summary: ICPD (undefined) + LMWH (standard prophylactic dose) versus IPCD (undefined)**

| 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 IPCD + LMWH standard dose versus IPCD (95% CI) |
| DVT | 334<br>(2 studies)<br>14-30 days | LOW[a]<br>due to risk of bias | RR 0.07<br>(0.02 to 0.26) | 63 per 1000 | 59 fewer per 1000<br>(from 47 fewer to 62 fewer) |
| PE | 334<br>(2 studies)<br>14-30 days | VERY LOW[a,b,c]<br>due to risk of bias, imprecision, indirectness | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 12 fewer to 12 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 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 Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

**Table 189: Clinical evidence summary: UFH versus no prophylaxis/mechanical**

| 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 UFH versus no prophylaxis (95% CI) |
| All-cause mortality | 393 (4 studies) 5-8 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.36 (0.1 to 1.27) | 46 per 1000 | 29 fewer per 1000 (from 41 fewer to 12 more) |
| DVT | 1991 (12 studies) 7-70 days | MODERATE[a] due to risk of bias | RR 0.40 (0.30 to 0.53) | 138 per 1000 | 83 fewer per 1000 (from 65 fewer to 97 fewer) |
| PE | 897 (10 studies) 7-70 days | LOW[a,b] due to risk of bias, imprecision | RR 0.60 (0.36 to 1.02) | 62 per 1000 | 25 fewer per 1000 (from 40 fewer to 1 more) |
| Major bleeding | 725 (7 studies) 6-14 days | LOW[a,b] due to risk of bias, imprecision | RR 1.30 (0.84 to 2.00) | 75 per 1000 | 23 more per 1000 (from 12 fewer to 75 more) |
| Fatal PE | 506 (4 studies) 7-70 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.15 (0 to 7.52) | 4 per 1000 | 3 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 confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

**Table 190: Clinical evidence summary: UFH versus IPCD (below knee)**

| 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 UFH versus IPCD (95% CI) |
| DVT | 265 (2 studies) 30 days | LOW[a,b] due to risk of bias, imprecision | RR 2.36 (0.87 to 6.44) | 38 per 1000 | 52 more per 1000 (from 5 fewer to 209 more) |
| PE | 265 | | Peto OR 1.04 | 8 per 1000 | 0 more 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 UFH versus IPCD (95% CI) |
| | (2 studies)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | (0.06 to 17) | | (from 7 fewer to 109 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 191: Clinical evidence summary: UFH versus VKA**

| 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 UFH versus VKA (95% CI) |
| DVT | 197<br>(2 studies)<br>time-point not reported | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.33<br>(0.11 to 1) | 122 per 1000 | 82 fewer per 1000<br>(from 109 fewer to 0 more) |
| Major bleeding | 100<br>(1 study)<br>time-point not reported | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 38 fewer to 38 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 Could not be calculated as there were no events in the intervention or comparison group
d Risk difference calculated in Review Manager

**Table 192: Clinical evidence summary: LMWH (low dose) versus no prophylaxis**

| Outcomes | No of | Quality of the evidence | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | effect (95% CI) | Risk with Control | Risk difference with LMWH low dose versus no prophylaxis (95% CI) |
|---|---|---|---|---|---|
| All-cause mortality | 183 (1 study) 42 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.12 (0.01 to 1.99) | 23 per 1000 | 20 fewer per 1000 (from 22 fewer to 22 more) |
| DVT | 183 (1 study) 42 days | LOW[a,b] due to risk of bias, imprecision | RR 0.26 (0.09 to 0.77) | 159 per 1000 | 118 fewer per 1000 (from 37 fewer to 145 fewer) |
| PE | 183 (1 study) 42 days | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | Peto OR 0.12 (0.01 to 1.99) | 23 per 1000 | 20 fewer per 1000 (from 22 fewer to 22 more) |
| Major bleeding | 183 (1 study) 42 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.93 (0.24 to 3.59) | 45 per 1000 | 3 fewer per 1000 (from 35 fewer to 118 more) |
| Thrombocytopaenia | 183 (1 study) 42 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 21 fewer to 21 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 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 Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

**Table 193: Clinical evidence summary: LMWH (low 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 Control | Risk difference with LMWH low dose versus UFH (95% CI) |
| All-cause mortality | 7018 (7 studies) 6-56 days | LOW[a,b] due to risk of bias, imprecision | RR 1.27 (0.93 to 1.73) | 19 per 1000 | 5 more per 1000 (from 1 fewer to 14 more) |
| DVT | 3045 (5 studies) 6-30 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.91 (1.22 to 3.00) | 18 per 1000 | 17 more per 1000 (from 4 more to 37 more) |
| PE | 6836 (7 studies) 6-30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.87 (0.41 to 1.83) | 4 per 1000 | 1 fewer per 1000 (from 3 fewer to 4 more) |
| Major bleeding | 6694 (7 studies) 5-30 days | VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision | RR 0.73 (0.49 to 1.11) | 52 per 1000 | 14 fewer per 1000 (from 26 fewer to 6 more) |
| Fatal PE | 5848 (5 studies) 6-30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.75 (0.54 to 5.71) | 1 per 1000 | 1 more per 1000 (from 1 fewer to 6 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 because heterogeneity, $I^2$=55%, p=0.04, unexplained by subgroup analysis.

**Table 194: Clinical evidence summary: LMWH (standard dose; standard duration) versus no prophylaxis/mechanical**

| 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 | 80<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.14<br>(0.01 to 2.26) | 49 per 1000 | 42 fewer per 1000<br>(from 48 fewer to 55 more) |
| DVT | 130<br>(2 studies)<br>7-30 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.35<br>(0.1 to 1.2) | 136 per 1000 | 89 fewer per 1000<br>(from 123 fewer to 27 more) |
| PE | 130<br>(2 studies)<br>14-30 days | VERY LOW[a,b,c]<br>due to risk of bias, imprecision | Peto OR 0.14<br>(0 to 7.17) | 15 per 1000 | 13 fewer per 1000<br>(from 15 fewer to 84 more) |
| Major bleeding | 527<br>(5 studies)<br>11-30 days | LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 2.90<br>(0.9 to 9.34) | 9 per 1000 | 16 more per 1000<br>(from 1 fewer to 67 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 if the outcome definition reported did not meet definition of outcome in protocol

**Table 195: Clinical evidence summary: LMWH (standard dose; standard duration) versus IPCD (undefined)**

| 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 low dose versus IPCD (95% CI) |
| DVT | 211 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.98 (0.2 to 19.23) | 9 per 1000 | 9 more per 1000 (from 8 fewer to 145 more) |
| PE | 211 (1 study) 30 days | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 18 fewer to 18 more)[e] |
| Thrombocytopaenia | 211 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.5 (0.09 to 2.7) | 38 per 1000 | 19 fewer per 1000 (from 34 fewer to 64 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 if the outcome definition reported did not meet definition of outcome in protocol
d Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

**Table 196: 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 Control | Risk difference with LMWH standard dose versus UFH (95% CI) |
| All-cause mortality | 2511 (5 studies) 8-30 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.04 (0.60 to 1.80) | 19 per 1000 | 1 more per 1000 (from 8 fewer to 15 more) |
| DVT | 2856 | | RR 0.85 | 40 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 LMWH standard dose versus UFH (95% CI) |
| | (8 studies)<br>7-56 days | LOW[a,b]<br>due to risk of bias, imprecision | (0.59 to 1.24) | | (from 16 fewer to 10 more) |
| PE | 3360<br>(8 studies)<br>7-56 days | MODERATE[a]<br>due to risk of bias | Peto OR 0.24<br>(0.08 to 0.73) | 7 per 1000 | 5 fewer per 1000<br>(from 2 fewer to 6 fewer) |
| Major bleeding | 3150<br>(8 studies)<br>8-30 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 1.69<br>(1.19 to 2.41) | 28 per 1000 | 19 more per 1000<br>(from 5 more to 39 more) |
| Fatal PE | 1002<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.13<br>(0.00 to 6.71) | 2 per 1000 | 2 fewer per 1000<br>(from 2 fewer to 11 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 197: 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 | 61<br>(1 study)<br>7 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 62 fewer to 62 more)[d] |
| DVT | 61<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | RR 0.19<br>(0.05 to 0.78) | 355 per 1000 | 287 more per 1000<br>(from 78 fewer to 337 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

| 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) |
| risk of bias<br>b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs<br>c Could not be calculated as there were no events in the intervention or comparison group<br>d Risk difference calculated in Review Manager | | | | | |

**Table 198: 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 Control | Risk difference with LMWH high dose versus UFH (95% CI) |
| All-cause mortality | 43<br>(1 study)<br>time-point not reported | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 87 fewer to 87 more)[d] |
| DVT | 43<br>(1 study)<br>time-point not reported | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 87 fewer to 87 more)[d] |
| Major bleeding | 43<br>(1 study)<br>time-point not reported | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 5.22<br>(0.68 to 39.74) | 50 per 1000 | 211 more per 1000<br>(from 16 fewer to 1000 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<br>b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs<br>c Could not be calculated as there were no events in the intervention or comparison group<br>d Risk difference calculated in Review Manager | | | | | |

**Table 199: Clinical evidence summary: LMWH (low 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 Control | Risk difference with LMWH low dose versus LMWH standard dose (95% CI) |
| All-cause mortality | 2931 (2 studies) 8-30 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.07 (0.7 to 1.62) | 29 per 1000 | 2 more per 1000 (from 9 fewer to 18 more) |
| DVT | 2853 (3 studies) 7-30 days | MODERATE[a] due to risk of bias | RR 1.98 (1.51 to 2.59) | 50 per 1000 | 49 more per 1000 (from 26 more to 80 more) |
| PE | 2853 (3 studies) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.15 (0.42 to 3.16) | 5 per 1000 | 1 more per 1000 (from 3 fewer to 10 more) |
| Major bleeding | 2966 (3 studies) 30 days | VERY LOW[a,b,c,d] due to risk of bias, inconsistency, indirectness, imprecision | RR 0.58 (0.14 to 2.41) | 16 per 1000 | 7 fewer per 1000 (from 14 fewer to 23 more) |
| Fatal PE | 35 (1 study) 30 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[e] | Not estimable[e] | 0 fewer per 1000 (from 106 fewer to 106 more)[f] |

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 heterogeneity, I2=66%, p=0.05, unexplained by subgroup analysis
d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
e Could not be calculated as there were no events in the intervention or comparison group
f Risk difference calculated in Review Manager

**Table 200: Clinical evidence summary: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)**

| Outcomes | No of | Quality of the | Relative effect | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | evidence (GRADE) | (95% CI) | Risk with Control | Risk difference with Extended duration LMWH standard dose versus standard duration LMWH standard dose (95% CI) |
|---|---|---|---|---|---|
| All-cause mortality | 501 (1 study) 60 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.51 (0.13 to 1.99) | 36 per 1000 | 18 fewer per 1000 (from 31 fewer to 36 more) |
| DVT | 332 (1 study) 25-31 days | LOW[a,b] due to risk of bias, imprecision | RR 0.43 (0.18 to 0.89) | 120 per 1000 | 68 fewer per 1000 (from 13 fewer to 98 fewer) |
| PE | 332 (1 study) 90 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.14 (0.01 to 2.19) | 12 per 1000 | 10 fewer per 1000 (from 12 fewer to 14 more) |
| Major bleeding | 928 (2 studies) up to 90 days | VERY LOW[a,b,c]= due to risk of bias, imprecision, inconsistency | Peto OR 0.83 (0.22 to 3.08) | 11 per 1000 | 2 fewer per 1000 (from 8 fewer to 21 more) |
| Fatal PE | 332 (1 study) 90 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.14 (0.00 to 6.90) | 6 per 1000 | 5 fewer per 1000 (from 6 fewer to 34 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 because heterogeneity, $I^2$=60%, p=0.12, unexplained by subgroup analysis.

**Table 201: 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 Control | Risk difference with Extended duration LMWH high dose versus standard duration LMWH high dose (95% CI) |

| 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 Extended duration LMWH high dose versus standard duration LMWH high dose (95% CI) |
| All-cause mortality | 488 (1 study) 90 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.29 (0.45 to 3.66) | 25 per 1000 | 7 more per 1000 (from 14 fewer to 67 more) |
| DVT | 488 (1 study) 28 days | LOW[a,b] due to risk of bias, imprecision | RR 0.63 (0.37 to 1.10) | 121 per 1000 | 45 fewer per 1000 (from 76 fewer to 12 more) |
| PE | 488 (1 study) 28 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 8 fewer to 8 more)[d] |
| Major bleeding | 625 (1 study) 22 days | LOW[b] due to imprecision | Peto OR 1.92 (0.20 to 18.54) | 3 per 1000 | 3 more per 1000 (from 3 fewer to 53 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 202: Clinical evidence summary: LMWH (standard dose; extended duration) + AES (undefined) versus LMWH (standard dose; standard duration) + AES (undefined)**

| Outcomes | No of | Quality of the | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | evidence (GRADE) | effect (95% CI) | Risk with LMWH standard dose standard duration + AES | Risk difference with LMWH standard dose extended duration + AES (95% CI) |
|---|---|---|---|---|---|
| All-cause mortality | 427 (1 study) 60 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.27 (0.69 to 2.36) | 77 per 1000 | 21 more per 1000 (from 24 fewer to 104 more) |
| DVT | 340 (1 study) 60 days | LOW[a,b] due to risk of bias, imprecision | RR 0.50 (0.26 to 0.95) | 149 per 1000 | 76 fewer per 1000 (from 9 fewer to 110 fewer) |
| PE | 343 (1 study) 28 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.14 (0.01 to 1.40) | 17 per 1000 | 14 fewer per 1000 (from 17 fewer to 7 more) |
| Fatal PE | 427 (1 study) 28 days | VERY LOW[a,b] due to risk of bias, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000 (from 9 fewer to 9 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 Could not be calculated as there were no events in the intervention or comparison group

d Risk difference calculated in Review Manager

**Table 203: Clinical evidence summary: Fondaparinux 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 Control | Risk difference with Fondaparinux versus LMWH standard dose (95% CI) |
| All-cause mortality | 2858 (1 study) 32 days | LOW[a,b] due to risk of bias, | RR 0.72 (0.48 to 1.08) | 39 per 1000 | 11 fewer per 1000 (from 20 fewer to 3 more) |

| 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 Fondaparinux versus LMWH standard dose (95% CI) |
| | | imprecision | | | |
| DVT | 2042 (1 study) 32 days | LOW[a,b] due to risk of bias, imprecision | RR 0.72 (0.49 to 1.06) | 58 per 1000 | 16 fewer per 1000 (from 30 fewer to 3 more) |
| PE | 2927 (1 study) 32 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 7.38 (0.46 to 118.03) | 0 per 1000 | Not estimable[c] |
| Major bleeding | 2858 (1 study) 5-11 days | LOW[a,b] due to risk of bias, imprecision | RR 1.43 (0.93 to 2.21) | 24 per 1000 | 10 more per 1000 (from 2 fewer to 29 more) |
| Fatal PE | 2927 (1 study) 32 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1 (0.2 to 4.95) | 2 per 1000 | 0 fewer per 1000 (from 2 fewer to 8 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 comparison group

**Table 204: Clinical evidence summary: Fondaparinux + IPCD (undefined) versus IPCD (undefined)**

| 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 Fondaparinux + IPCD versus IPCD (95% CI) |
| All-cause mortality | 1285 (1 study) | LOW[b] | Peto OR 1.63 (0.55 to 4.86) | 8 per 1000 | 5 more per 1000 (from 3 fewer to 29 more) |

| 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 Fondaparinux + IPCD versus IPCD (95% CI) |
| | 32 days | due to imprecision | | | |
| DVT | 842<br>(1 study)<br>10 days | MODERATE[a]<br>due to risk of bias | RR 0.31<br>(0.14 to 0.73) | 53 per 1000 | 36 fewer per 1000<br>(from 14 fewer to 45 fewer) |
| PE | 1285<br>(1 study)<br>32 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 0.36<br>(0.05 to 2.57) | 6 per 1000 | 5 fewer per 1000<br>(from 7 fewer to 11 more) |
| Fatal PE | 1285<br>(1 study)<br>32 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | Peto OR 1.02<br>(0.06 to 16.39) | 2 per 1000 | 0 more per 1000<br>(from 1 fewer to 23 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 205: Fondaparinux versus no prophylaxis/mechanical**

| 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 Fondaparinux + IPCD versus IPCD (95% CI) |
| Major bleeding | 1285<br>(1 study)<br>32 days | MODERATE[a]<br>due to risk of bias | Peto OR 5.33<br>(1.63 to 17.45) | 2 per 1000 | 7 more per 1000<br>(from 1 more 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

**Table 206: Fondaparinux + UFH + mechanical (AES + IPCD) versus LMWH + UFH + mechanical (AES + IPCD)**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH + UFH + mech | Risk difference with Fonda + UFH + mech (95% CI) |
| PE | 258 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.13 (0.01 to 2.13) | 16 per 1000 | 14 fewer per 1000 (from 15 fewer to 17 more) |
| Major bleeding | 298 (1 study) time-point not reported | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 1.88 (0.19 to 18.21) | 7 per 1000 | 6 more per 1000 (from 6 fewer to 105 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 207: VKA versus no 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) |
| DVT | 96 (1 study) 7 days | LOW[a,b] due to risk of bias, imprecision | RR 0.27 (0.08 to 0.92) | 229 per 1000 | 167 fewer per 1000 (from 18 fewer to 211 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

## 35.4 Economic evidence

**Published literature**

Two original economic models were developed for this population in CG92.[224] Additionally, one health economic study was also identified with the relevant comparison and has been included in this review.[305] These are summarised in the health economic evidence profiles below (Table 208, Table 209 and Table 210) and the health economic evidence tables in appendix J.

An economic model was developed for this population in CG46; for both standard duration and post-discharge prophylaxis. Both these models were selectively excluded due to the availability of the more applicable model from CG92. [224] Additionally, three economic studies relating to this review question were previously included in CG46, [226] but one was excluded due to methodological limitations,[219] and the other two were selectively excluded due to the availability of more applicable evidence.[121,253] These are listed in appendix O, with reasons for exclusion given.

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

**Table 208: Health economic evidence profile: LMWH (standard dose, standard duration) + AES (knee-length) vs LMWH (standard dose , standard duration) + AEs (thigh-length ) vs LMWH (standard dose, standard duration)**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Wade 2015[305] ([UK]) | Directly applicable [(a)] | Potentially serious limitations [(b)] | - **Study design**: CUA using decision modelling<br>- **Population**: Patients undergoing any general surgery (subgroups considered were high risk patients, medium risk patients and low risk patients).<br>- **Interventions:**<br>**Intervention 1:**<br>LMWH (for duration of 7 days (standard duration).<br>**Intervention 2:**<br>Knee-length AES in addition to LMWH for a duration of 7 days (standard duration).<br>**Intervention 3:**<br>Thigh-length AES in addition to pharmacological prophylaxis (LMWH) for duration of 7 days (standard duration). | **High risk patients:**<br>1 (vs 3) : £176<br>2 (vs 3): £177<br>3: comparator<br><br>**Intermediate risk patients:**<br>1 (vs 3) : £46<br>2 (vs 3): £76<br>3: comparator<br><br>**Low risk patients:**<br>1:comparator)<br>2 (vs 1) : £35<br>3 (vs 1): £5 | **High risk patients:**<br>1 (vs 3): 0.009 QALYs lost<br>2 (vs 3) : 0.007 QALYs lost<br>3: comparator<br><br>**Intermediate risk patients:**<br>1 (vs 3):0.004 QALYs lost<br>2 (vs 3): 0.003 QALYs lost<br>3 : comparator<br><br>**low risk patients:**<br>1: Comparator<br>2 (vs 1) : 0.002 QALYs lost<br>3 (vs 1): 0.002 | **High risk patients:**<br>LMWH + thigh-length AES (intervention 3) dominant (less costly and more effective)<br><br>**Intermediate risk patients:**<br>LMWH + thigh-length AES (intervention 3) dominant (less costly and more effective)<br><br>**Low risk patients:**<br>LMWH + thigh-length AES (intervention 3) cost effective<br>(ICER: £2,632 per QALY gained vs LMWH alone [intervention 1]) | The results of all scenario and sensitivity analyses were largely consistent with the base case analysis for all subgroups |

*Abbreviations: AES: anti-embolism stockings; CUA: cost utility analysis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; QALY: quality-adjusted life years; RCT: randomised controlled trial*

*a) Mixed population of all surgery types, however subgroup analysis is also presented.*

*b) The model did not include some relevant health outcomes; e.g. clinically-relevant non-major bleeding , minor bleeding and surgical site infection.*

**Table 209: Health economic evidence profile: pharmacological, mechanical or combination of prophylaxis strategies vs each other**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| National Guideline Centre 2010[224] ([UK]) | Partially applicable [(a)] | Potentially serious limitations [(b)] | - **Study design:** CUA using decision analytic model based on NMAs<br>- **Population:** Adult (18 years or older) admitted for elective abdominal surgery to hospitals in England.<br>- **Interventions:**<br>1. AES<br>2. IPCD-FID<br>3. UFH+ AES<br>4. LMWH+ AES<br>5. LMWH<br>6. Aspirin high dose<br>7. UFH<br>8.Fondaparinux+ IPCD-FID<br>9.Fondaparinux<br>10.VKA<br>11.No prophylaxis<br>12.UFH+ Aspirin high dose | NR | NR | **Incremental net benefit:**<br><br>Intervention 1: £488<br>Intervention 2: £464<br>Intervention 3: £408<br>Intervention 4: £348<br>Intervention 5: £347<br>Intervention 6: £314<br>Intervention 7: £241<br>Intervention 8: £127<br>Intervention 9: £104<br>Intervention 10: £75<br>Intervention 11: £0<br>Intervention 12: -£694 | High- dose aspirin alone was the most cost effective strategy when the population specific pulmonary embolism relative risks were used.<br>The results were highly sensitive to baseline risk of major bleeding and baseline risk of pulmonary embolism. For patients at lowest risk of major bleeding, combination prophylaxis is cost-effective, rather than mechanical prophylaxis alone. |

*Abbreviations: AES: Anti-embolism stockings; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; DVT: deep vein thrombosis; FID: foot impulse devices; HD: high dose; HIT: Heparin induced thromboembolism; ICER: incremental cost-effectiveness ratio; IPCD: intermittent pneumatic compression device; 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; VKA: Vitamin K antagonists.*

*(a) Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context. Some interventions are not included in our review protocol (aspirin (high dose))*

*(b) The relative treatment effect applied to all VTE events in the model is the relative treatment effect obtained from the DVT NMA.*

**Table 210: Health economic evidence profile: LMWH (post-discharge) vs no post-discharge prophylaxis**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| National Guideline Centre 2010[224] ([UK]) | Directly applicable [(a)] | Potentially serious limitations [(b)] | - **Study design:** CUA using decision analytic model based on pairwise Meta-analysis<br>- **Population:** Adult (18 years or older) admitted for elective abdominal surgery to hospitals in England ; randomised 10 to 12 days after surgery (mainly cancer surgery patients)<br>- **Interventions:**<br>**Intervention 1:**<br>No post discharge prophylaxis<br><br>**Intervention 2:**<br>LMWH initiated post discharge and continued for 21 days. | NR | NR | **Incremental net benefit:**<br>No prophylaxis**:** £0 (comparator)<br>LMWH (post-discharge)**:** £49 | The result was consistent for all deterministic sensitivity analyses. In the probabilistic sensitivity analysis, LMWH was more cost-effective in 77% of the 5000 simulations of the probabilistic sensitivity analysis.<br>It was also found that life expectancy would have to be halved for it to no longer be cost-effective for these patients |

*Abbreviations: CUA: cost utility analysis; DVT: deep vein thrombosis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; MB: major bleeding; MA: meta-analysis; PE: pulmonary embolism; QALY: quality-adjusted life years; RCT: randomised controlled trial; 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 MA.*

## 35.5 Evidence statements

**Clinical**

**Pairwise meta-analysis statements**

**Mechanical prophylaxis versus mechanical prophylaxis**

*AES*

Two studies (n=291) evaluated the use of above knee AES compared to no prophylaxis. A clinical benefit of AES was found for DVT, and a possible clinical benefit was found for PE, although for this outcome there was very serious imprecision around the estimate. No clinical difference was found for all-cause mortality. The evidence ranged from very low to moderate quality due to risk of bias and imprecision.

One study (n=95) compared below knee AES to no prophylaxis and found a possible clinical benefit of stockings in terms of DVT. However there was very serious imprecision, and therefore the estimate is also consistent with no difference and clinical harm. The evidence was very low quality due to risk of bias and imprecision.

One study compared AES at an undefined length to no VTE prophylaxis. The evidence showed that for the outcome of DVT, there was a clinical benefit of AES. Evidence for this comparison was of moderate quality due to risk of bias.

One study (n=114) compared above knee AES with below knee AES. For the only reported outcome of DVT, there was a possible clinical harm of above knee AES, however there was very serious imprecision around the estimate and therefore was also consistent with no difference and clinical benefit. The evidence for this comparison was of very low quality due to risk of bias and imprecision.

*Foot pump*

One study of 66 participants evaluated the use of foot pumps compared to no prophylaxis. The evidence demonstrated a possible clinical benefit of foot pumps in terms of both all-cause mortality and DVT, however imprecision around these estimates was also consistent with no difference and in the case of mortality, also possible harm as well. The quality of evidence for this comparison ranged from low to very low due to risk of bias and imprecision.

*IPCD*

Four studies evaluated IPCD (below knee) versus no prophylaxis. A possible clinical benefit of IPCD was found for both DVT and fatal PE, however for both of these outcomes there was very serious imprecision around the estimate, and therefore was also consistent with no difference and clinical harm. No clinical difference was found for all-cause mortality, and there was a suggested clinical harm of IPCD in terms of PE. Again, both of these outcomes had serious imprecision around the estimate. The evidence for this comparison was very low due to risk of bias, imprecision, and for the DVT outcome, inconsistency.

One study (n=90) evaluated the use of IPCD (full leg) compared to IPCD (below knee). The evidence showed a possible clinical benefit of full leg IPCD in terms DVT and fatal PE, but a suggested clinical harm for full leg IPCD in terms of PE. Quality was very low due to risk of bias and imprecision.

**Pharmacological prophylaxis versus pharmacological prophylaxis**

*UFH*

Two studies evaluated the use UFH versus VKA in terms of DVT (n=197). A possible clinical benefit was found for UFH, however there was serious imprecision around the estimate and therefore evidence was also consistent with no difference. One study reported the outcome of major bleeding

(n=100). No clinical difference was found between UFH and VKA, however there was very serious imprecision which meant that this was also consistent with clinical benefit and clinical harm. The evidence quality ranged from low to very low due to risk of bias and imprecision.

*LMWH (low dose)*

One study compared LMWH at a low dose with no prophylaxis (n=183). There was a suggested clinical benefit for LMWH for all-cause mortality, DVT and PE. There was no clinical difference for major bleeding and thrombocytopaenia. Quality ranged from very low to low due to risk of bias, imprecision and for one outcome, indirectness.

LMWH at a low dose was compared to UFH. Seven studies reported the outcomes all-cause mortality, PE and major bleeding (n=6694-7018). The evidence demonstrated a possible clinical harm of LMWH for all-cause mortality, and a possible clinical harm for major bleeding. Both outcomes had serious imprecision around the estimate, and therefore were also consistent with no difference. There was no clinical difference between LWMH and UFH in terms of PE, with very serious imprecision consistent with clinical benefit and clinical harm. Five studies reported the outcomes DVT and fatal PE (n=3045-5848). Evidence from these studies showed a possible clinical harm for both outcomes, however there was serious and very serious imprecision around the estimates. The quality of the evidence ranged from very low to low due to risk of bias, imprecision and inconsistency.

LMWH at a low dose was compared to LMWH at a standard dose. Two studies reported the outcome all-cause mortality (n=2931). The evidence demonstrated a possible clinical harm of low dose LMWH, however there was very serious imprecision consistent with no difference and benefit. Three studies reported the outcomes DVT, PE and major bleeding (n=2853-2966). There was a possible clinical harm of low dose LMWH in terms of DVT, no clinical difference in terms of PE, and a possible clinical benefit of low dose LMWH in terms of major bleeding. All outcomes had very serious imprecision. One study reported the outcome fatal PE (n=35). This study demonstrated no clinical difference between the two doses of LMWH, however there was very serious imprecision consistent with both harm and benefit. Evidence for the comparison ranged from very low to moderate quality, due to risk of bias, imprecision and, for the major bleeding outcome, indirectness and inconsistency.

*LMWH (standard dose)*

For the comparison of LWMH (standard dose) versus UFH, eight studies reported the outcomes DVT, PE and major bleeding. There was a possible clinical benefit of LMWH for PE, no clinical difference for DVT, and a suggested clinical harm of LMWH for major bleeding. The DVT outcome had serious imprecision around the estimate consistent with benefit, whereas the major bleeding outcome demonstrated serious imprecision consistent with no difference. Five studies reported the outcome all-cause mortality. No clinical difference between LMWH and UFH was found, however there was very serious imprecision around the estimate, and therefore was consistent with clinical harm and clinical benefit. One study reported fatal PE, and found a possible clinical benefit of LMWH, however this outcome had very serious imprecision consistent with no difference and clinical harm. The evidence ranged from low to very low quality due to risk of bias, imprecision, and inconsistency.

Standard dose LMWH at an extended duration was compared to standard dose LMWH at a standard duration. One study reported the outcomes all-cause mortality, DVT, PE and fatal PE (n=332-501). A possible clinical benefit of extended duration LMWH was found for all-cause mortality, DVT, PE and fatal PE, however all outcomes had either serious or very serious imprecision around the estimate. Two studies reported the outcome major bleeding (n=928). There was no clinical difference for major bleeding, however there was very serious imprecision around the estimate consistent with both benefit and harm. The evidence ranged from very low to low quality due to risk of bias and imprecision.

*LMWH (high dose)*

One study evaluated LMWH at a high dose versus no prophylaxis. The evidence demonstrated a possible clinical benefit for LWMH was found for DVT. However there was serious imprecision around the estimate, and therefore evidence was also consistent with no difference. No clinical difference was found between LMWH and no prophylaxis in terms of all-cause mortality, however again there was very serious imprecision around the estimate. The evidence was of low quality due to risk of bias and imprecision.

For the comparison of LMWH at a high dose versus UFH, one study of 43 participants reported the outcomes all-cause mortality, DVT and major bleeding. There was no clinical difference between the two pharmacological prophylaxis methods for the all-cause mortality and DVT outcomes, although there was very serious imprecision around the estimate for both outcomes, which therefore were also consistent with benefit and harm. There was a possible clinical harm of LMWH in terms of major bleeding, with very serious imprecision around the estimate. The quality of the evidence was very low for all outcomes due to risk of bias and imprecision.

One study compared high dose LMWH at an extended duration versus high dose LMWH at a standard duration (n=488-625). A possible clinical benefit of extended duration LMWH was found for DVT, however there was serious imprecision around the estimate and therefore was also consistent with no difference. A possible clinical harm was found for all-cause mortality and major bleeding however there was very serious imprecision consistent with no difference and benefit. There was no clinical difference for PE, with very serious imprecision consistent with both benefit and harm. The evidence ranged from very low to low quality due to risk of bias and imprecision.

*Fondaparinux*

One study compared fondaparinux to LMWH at a standard dose (n=2042-2927). A possible clinical benefit was found for fondaparinux in terms of all-cause mortality, and DVT. Both outcomes had serious imprecision around the estimate and so were also consistent with no difference. A possible clinical harm was found for PE and major bleeding. Very serious imprecision around the estimate for PE meant that it is also consistent with no difference and benefit, and serious imprecision around the estimate for major bleeding meant that the outcome is also consistent with no difference. No clinical difference was found for fatal PE, with very serious imprecision. The evidence ranged from low to very low quality due to risk o bias and imprecision.

*VKA*

One study compared VKA with no prophylaxis (n=96). For the outcome of DVT, there was a possible clinical benefit of VKA, however there was serious imprecision around the estimate and therefore this was also consistent with no difference. The evidence was low quality due to risk of bias and imprecision.

**Mechanical prophylaxis versus pharmacological prophylaxis**

One study compared above knee AES with UFH (n=97). There was a possible clinical benefit of AES in terms of fatal PE, however there was very serious imprecision around the estimate consistent with no difference and harm. The evidence was very low quality due to risk of bias and imprecision.

One study compared below knee AES with UFH (n=159). No clinical difference was found for both all-cause mortality and PE, with very serious imprecision consistent with both benefit and harm. The evidence was of very low quality due to risk of bias, imprecision and, for the PE outcome, indirectness.

One study of 100 participants compared electrical stimulation with UFH. There was a possible clinical harm of electrical stimulation in terms of DVT, however there was very serious imprecision consistent with benefit and no difference. The evidence was of very low quality due to risk of bias and imprecision.

One study compared full leg IPCD versus VKA (n=100). A possible clinical harm of ICPD was found for DVT and PE. For both outcomes there was very serious imprecision around the estimate consistent with benefit and no difference. There was no clinical difference for all-cause mortality, again with very serious imprecision. The evidence was very low quality due to risk of bias and imprecision.

**Pharmacological prophylaxis versus mechanical prophylaxis**

UFH was compared to no prophylaxis/mechanical prophylaxis. Twelve studies reported the outcome DVT (n=1991), and the evidence demonstrated a clinical benefit for UFH. Ten studies reported the outcome PE (n=897). There was a possible clinical benefit of UFH, however there was serious imprecision, and was therefore also consistent with no clinical difference. Seven studies reported the outcome major bleeding (n=725). This demonstrated a possible clinical harm of UFH, with serious imprecision consistent with no difference. Four studies reported the outcomes all-cause mortality and fatal PE (n=393-506). There was a possible clinical benefit of UFH for both outcomes, however both outcomes also had very serious imprecision around the estimate and were consistent with no difference and clinical harm. The evidence ranged from very low to moderate quality due to risk of bias and imprecision.

Standard dose LMWH was compared to no prophylaxis/mechanical prophylaxis. One study reported the outcome all-cause mortality (n=80). There was a possible clinical benefit of LMWH for this outcome, however there was very serious imprecision around the estimate and so this was also consistent with harm and no difference. Two studies reported DVT and PE (n=130). There was a possible clinical benefit of LMWH for both outcomes, however there was serious and very serious imprecision around the estimates, consistent with no difference, and no difference and clinical harm. Five studies reported the outcome major bleeding (n=527). The evidence demonstrated a possible clinical harm of LMWH for this outcome, however there was serious imprecision which was also consistent with no difference. The evidence was very low to low quality due to risk of bias and imprecision.

One study compared fondaparinux to no prophylaxis/mechanical prophylaxis (n=1285). There was a clinical harm of fondaparinux in terms of DVT. No other outcomes were reported. The evidence was high quality.

Two studies compared UFH and below knee IPCD (n=265). A possible clinical harm was found for UFH in terms of DVT, however there was serious imprecision around the estimate and therefore was also consistent with no difference. No clinical difference was found for PE, however there was very serious imprecision around the estimate consistent with both benefit and harm. The evidence ranged from very low to low quality due to risk of bias and imprecision.

One study compared standard dose LMWH to IPCD at an undefined length (n=211). The evidence demonstrated a possible clinical harm of LMWH in terms of DVT, however there was very serious imprecision around the estimate consistent with no difference and benefit. There was no clinical difference in terms of PE, with very serious imprecision consistent with both benefit and harm. For the outcome of thrombocytopaenia, a possible clinical benefit of LWMH was found, however there was also very serious imprecision consistent with no difference and harm. The evidence was very low quality due to risk of bias and imprecision.

**Combination prophylaxis versus combination prophylaxis or single-prophylaxis agents**

*AES*

One study compared below knee AES in combination with UFH to below knee AES alone (n=163). There was no clinical difference between the interventions for both all-cause mortality and PE, however there was very serious imprecision for both outcomes consistent with both benefit and harm. The evidence was very low quality due to risk of bias and inconsistency.

Above knee AES in combination with UFH was compared to UFH alone. One study reported the outcomes all-cause mortality and fatal PE (n=160-176). A possible clinical harm was found for the combination intervention in terms of all-cause mortality, however there was very serious imprecision around the estimate, and therefore this was also consistent with no difference and benefit. A possible clinical benefit was seen for the combination in terms of fatal PE, however again there was very serious imprecision consistent with no difference and harm. Two studies reported the outcomes DVT and PE (n=336). There was a clinical benefit of the combination intervention in terms of DVT, and a possible clinical benefit in terms of PE, although this outcome estimate had very serious imprecision and was consistent with no difference and harm. The evidence ranged from very low to moderate quality due to risk of bias and imprecision.

One study compared below knee AES in combination with UFH to UFH alone (n=174). The evidence showed no clinical difference for all-cause mortality or PE. Both outcomes had very serious imprecision around the estimate and therefore were also consistent with both benefit and harm. The evidence was very low quality due to risk of bias, imprecision and, for the PE outcome, indirectness.

One study compared the combination of above knee AES and full leg IPCD with above knee AES alone (n=77). There was a possible clinical benefit of the combined interventions for DVT, however there was very serious imprecision around the estimate and this was therefore also consistent with no difference and harm. There was no clinical difference in terms of PE, however there was very serious imprecision consistent with both benefit and harm. The evidence was very low quality due to risk of bias and imprecision.

One study compared AES at an undefined length in combination with full leg IPCD to AES alone (n=108). There was a possible clinical benefit of the combined interventions in terms of DVT, however there was serious imprecision consistent with no difference. There was no clinical difference in terms of PE, with very serious imprecision around the estimate, consistent with both harm and benefit. The evidence ranged from very low to low quality due to risk of bias and imprecision.

One study compared AES at an undefined length in combination with full leg IPCD to UFH alone (n=100). There was a possible clinical benefit of the combined intervention in terms of DVT, however there was very serious imprecision around the estimate and therefore was also consistent with no difference and harm. No other outcomes were reported. The evidence was very low quality due to risk of bias and imprecision.

One study compared AES at an undefined length in combination with full leg IPCD to electrical stimulation alone (n=100). There was a possible clinical benefit of the combined intervention in terms of DVT, however there was serious imprecision around the estimate consistent with no difference. No other outcomes were reported. The evidence was low quality due to risk of bias and imprecision.

*Foot impulse device*

One study compared the combination of FID, below knee IPCD and low dose LMWH to the combination of FID and below knee IPCD. A possible clinical benefit was found for both DVT and PE, however with very serious and serious imprecision around the estimates. No clinical difference was found in terms of thrombocytopaenia, however there was very serious imprecision consistent with both benefit and harm. The evidence was very low to low quality due to risk of bias , imprecision and, for the DVT outcome, indirectness.

*IPCD*

Two studies compared IPCD at an undefined length in combination with standard dose LMWH with IPCD at an undefined length alone (n=334). The evidence showed a clinical benefit of the combination intervention in terms of DVT. There was no clinical difference in terms of PE, however

there was very serious imprecision around the estimate for this outcome, and therefore was consistent with both benefit and harm. The evidence ranged from very low to low quality due to risk of bias, imprecision, and for the PE outcome, indirectness.

*LMWH*

One study compared standard dose and extended duration LMWH in combination with AES at an undefined length, to standard dose and standard duration LMWH in combination with AES at an undefined length (n=343-427). There was a possible clinical harm of the extended duration LMWH combination in terms of all-cause mortality, however there was very serious imprecision around the estimate and so this was also consistent with benefit and no difference. There was a possible clinical benefit for both DVT and PE. Both outcomes also had serious and very serious imprecision around the estimate. There was no clinical difference in terms of fatal PE. This outcome had very serious imprecision around the estimate consistent with both harm and benefit. The evidence ranged from very low to low quality due to risk of bias and imprecision.

*Fondaparinux*

One large study compared fondaparinux in combination with IPCD at an undefined length, to IPCD at an undefined length alone (n=842-1285). There was a possible clinical harm of the fondaparinux + IPCD combination in terms of all-cause mortality, however there was very serious imprecision around the estimate and therefore this was also consistent with benefit and no difference. There was a clinical benefit of the combined intervention in terms of DVT, and a possible benefit in terms of PE, although this was also consistent with no difference and clinical harm. There was no clinical difference in terms of fatal PE, although due to very serious imprecision around the estimate this was also consistent with both benefit and harm. The evidence ranged from very low to moderate quality due to risk of bias and imprecision.

One study compared fondaparinux in combination with UFH and mechanical prophylaxis (AES and IPCD), to standard dose LMWH in combination with UFH and mechanical prophylaxis (AES and IPCD) (n=258-298). There was a possible clinical benefit of the fondaparinux combination intervention in terms of PE, however there was very serious imprecision consistent with no difference and clinical harm. There was a possible clinical harm in terms of major bleeding, however there was very serious imprecision around the estimate, and therefore was also consistent with no difference and benefit. The evidence was very low quality due to risk of bias and imprecision.

**Network meta-analysis statements**

*DVT (symptomatic and asymptomatic)*

48 studies were included in the network meta-analysis (NMA) for the outcome of DVT (symptomatic and asymptomatic), involving 22 treatments. Treatments included no VTE prophylaxis, pharmacological and mechanical interventions as single agents as well as combination interventions of both pharmacological and mechanical interventions. Results from the network meta-analysis presented LMWH at a standard dose for a standard duration initiated post-operatively in combination with IPCD, fondaparinux in combination with IPCD, and AES (above-knee) in combination with IPCD (full leg) as the most clinically effective interventions in terms of the outcome of DVT (symptomatic and asymptomatic). The least clinically effective interventions were no prophylaxis, VKA and LMWH at a low dose for a standard duration initiated pre-operatively. One inconsistency was identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a considerable amount of uncertainty around the rank-point estimates with considerably wide credible intervals.

*PE*

26 studies were included in the NMA for the outcome of PE, involving 13 treatments. Treatments included no VTE prophylaxis, pharmacological and mechanical interventions as single agents as well as combination interventions of both pharmacological and mechanical interventions. Results from the network meta-analysis presented LMWH at a standard dose for an extended duration initiated pre-operatively, AES (above knee), LMWH at a standard dose for a standard duration initiated by post-operatively as the most clinically effective interventions in terms of the outcome of PE. The least clinically effective interventions were IPCD (full leg), fondaparinux and IPCD (below knee). No inconsistencies were identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a high amount of uncertainty around the rank-point estimates with very wide credible intervals.

*Major bleeding*

24 studies were included in the NMA for the outcome of major bleeding, involving 15 treatments. Treatments included no VTE prophylaxis and pharmacological interventions (mechanical interventions were combined with no prophylaxis as the assumption was made that these interventions do not contribute to bleeding risk). Results from the network meta-analysis presented no prophylaxis, LMWH at a low dose for a standard duration initiated pre-operatively and UFH as the most clinically effective interventions in terms of major bleeding. The least clinically effective interventions were LMWH at a high dose for a standard duration initiated pre-operatively, fondaparinux and LMWH at a standard dose for a standard duration initiated post-operatively. One inconsistency was identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a high amount of uncertainty around the rank-point estimates with considerably wide credible intervals across a majority of the interventions.

**Economic**

- One cost-utility analysis found that for VTE prophylaxis:
  - In low risk general surgery patients, LMWH (standard dose, standard duration) + thigh-length AES was cost effective compared to LMWH (standard dose, standard duration) alone (ICER: £2,632 per QALY gained)
  - In intermediate and high risk general surgery patients, LMWH (standard dose, standard duration) + thigh-length AES was dominant (less costly and more effective) compared to LMWH (standard dose, standard duration) alone

  This analysis was assessed as directly applicable with potentially serious limitations
- One cost-utility analysis found that in people admitted for general surgery AES was the most cost-effective intervention (having the highest incremental net monetary benefit [INMB]) compared to no prophylaxis ( INMB: £488). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that post-discharge LMWH (standard dose) was cost effective (INMB: £49) compared to no post-discharge prophylaxis in patients admitted for general surgery. This analysis was assessed as directly applicable with potentially serious limitations.

## 35.6 Recommendations and link to evidence

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| **Recommendations** | **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]** |

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| | **1.5.38 Start mechanical VTE prophylaxis on admission for people undergoing abdominal surgery. Choose either:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression. [2018]**<br><br>**Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [2018]**<br><br>**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:**<br>• **LMWH[aa] or**<br>• **fondaparinux sodium[bb]. [2018]**<br><br>**1.5.40 Consider extending pharmacological VTE prophylaxis to 28 days postoperatively for people who have had major cancer surgery in the abdomen. [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 (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.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Sixty-seven randomised controlled trials were included in this review. Sixty-two of these were included in the previous guideline (CG92). Five new studies were added to the review. A total of thirty-nine comparisons were included in this review, evaluating the use of pharmacological (UFH, LMWH, VKA and fondaparinux) and mechanical (AES, IPCD, foot pump, FID and electrical stimulation) interventions for VTE prophylaxis.<br>For the majority of evidence in this review, the quality ranged from a GRADE rating of moderate to very low. This was due to a lack of blinding, presence of selection bias, incomplete outcome reporting due to the high number of drop outs in some |

[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), 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.

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| | included studies, and use of inadequate or unreported method of measurement, resulting in a high or very high risk of bias rating. Furthermore, much of the evidence in the review had serious or very serious imprecision, leading to further downgrading to the quality of evidence. A high quality GRADE rating was seen for one outcome, in the fondaparinux versus no prophylaxis/mechanical prophylaxis comparison, for the DVT outcome. |
| Trade-off between clinical benefits and harms | The committee noted that the review contains both open and laparoscopic surgery populations, and that these populations were likely to have different mobilisation times and associated risks. The committee discussed creating separate recommendations for these populations but recognised that it would be difficult to align a distinction in recommendations in line with the risk assessment recommendations, given that not all laparoscopic procedures are under 90 minutes, and given the fact that many of the included studies did not separate the two populations as they either used a mix of laparoscopic and open surgery procedures, or did not specify the type of procedure used.<br><br>**Mechanical prophylaxis**<br><br>The committee noted that there was no evidence for foot impulse devices as a standalone intervention and therefore a positive recommendation for the use of this intervention for VTE prophylaxis could not be made. The committee also discussed the evidence for the use of AES. It was considered that while there was no convincing evidence that above knee AES was better than below knee, the economic evidence suggested a slight benefit for above knee AES. Therefore, the committee agreed there was insufficient evidence to specify one particular option of above or below knee AES in the recommendations. In terms of IPCD the committee discussed the practical considerations that need to be taken into account with respect to mobilising the patient. IPCD are usually used only during the surgery. Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a patient is mobile.<br><br>**Pharmacological prophylaxis**<br><br>The committee considered the evidence for pharmacological prophylaxis. The committee noted that there was evidence to support LMWH and fondaparinux as being better than no prophylaxis. However there was not sufficient evidence to determine whether LMWH was better than fondaparinux. For prevention of DVT the evidence suggested that pharmacological prophylaxis (LMWH or fondaparinux) in combination with IPCD may be of most clinical benefit.<br><br>The network meta-analysis (NMA) conducted showed that combination prophylaxis strategies with pharmacological and mechanical interventions are more clinically beneficial in terms of reducing DVT. These combination strategies had higher rankings compared to pharmacological or mechanical interventions as standalone interventions, particularly LMWH at a standard dose for a standard duration initiated post-operatively in combination with IPCD which was ranked as the most clinically effective prophylaxis in the NMA for DVT. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials was between 7 and 10 days. The committee agreed this should be extended to 28 days for cancer surgery because the evidence identified was for this duration. |
| Trade-off between net clinical effects and costs | Two economic studies were included in this review. One is an economic evaluation recently published as part of an HTA funded study. This was assessed as directly applicable with minor limitations. The other was the economic model previously developed for CG92 which covered two comparisons; one for standard duration prophylaxis options and the second for post-discharge prophylaxis. The model comparing standard duration prophylaxis options was assessed as partially applicable with potentially serious limitations. The model for post-discharge prophylaxis was assessed as directly applicable with potentially serious limitations. Additionally, four studies were selectively excluded; one was excluded due to |

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| | methodological limitations, three (including the model developed for CG46) were selectively excluded due to the availability of the more applicable included studies.<br><br>The first of the two included studies was an economic model that compared above and below knee AES; each combined with LMWH (standard dose and standard duration), vs LMWH alone. The results were presented for three levels of baseline risk of VTE: high, intermediate and low. For people at high or intermediate risk of VTE, LMWH + thigh-length AES was the dominant option. For people at low risk, LMWH + thigh-length AES was the cost effective option with an ICER of £2,632 per QALY gained compared to LMWH alone.<br><br>Two models were developed in CG92. The first was for standard duration prophylaxis and included the following interventions: AES, IPCD-FID, UFH (standard dose)+AES, LMWH (standard dose)+ AES, LMWH (standard dose), Aspirin (high dose), UFH (standard dose), Fondaparinux+ IPCD-FID, Fondaparinux, VKA (variable dose), UFH (standard dose) + Aspirin (high dose), and no prophylaxis. The committee noted that not all of these interventions are still relevant to current practice (for example aspirin [high dose] and VKA). Mechanical prophylaxis with either AES or IPCD were the most cost effective options in the base case analysis with INMB of £488 and £464 respectively. However in a two-way sensitivity analysis that varied the baseline risk of PE and MB, combined prophylaxis of LMWH+ stocking was the most cost-effective option for high baseline risk of PE and low risk of major bleeding.<br><br>The second model compared post-discharge prophylaxis with LMWH with no prophylaxis. The results showed that extending the duration of LMWH prophylaxis to continue post-discharge was cost effective compared to no prophylaxis with an INMB of £49.<br><br>The committee considered the economic evidence presented, alongside the clinical evidence. The committee noted that, in line with CG92 recommendation, combined prophylaxis for people at high risk of VTE is the most cost effective option. This was supported by the newly published HTA report that stratified surgical patients according to their level of VTE risk; where combined prophylaxis was the most cost effective option.<br><br>The committee considered the recent clinical evidence and determined that both LMWH and fondaparinux were better compared to no prophylaxis; however, no clear conclusion could be made in terms of superiority of one over the other. However, as low quality clinical evidence for the DVT outcome suggested superiority of fondaparinux, the committee considered that this would justify the increased cost, and the choice of either as pharmacological prophylaxis options should be made based on the baseline bleeding risk.<br><br>The committee discussed whether the evidence was enough to recommend either knee or thigh length AES. The economic evidence supported the cost effectiveness of combined prophylaxis that includes thigh length AES, however the committee noted that thigh length AES are less convenient for people to wear and are more difficult to fit. Hence, the committee agreed that the choice of the length of stocking should be made taking into account the preference of the individual and his/her ability to adhere to wearing them. No studies were identified that compared thigh versus knee length for IPCD, so the committee considered that, similar to AES, the choice of the length should be based on preference, likelihood of adherence and ease of fitting.<br><br>The committee also discussed the duration of prophylaxis and noted that the economic model developed for CG92 supported extending the duration of prophylaxis for those who are at increased risk of VTE. These were primarily people undergoing surgeries for cancer. For this population, continuing LMWH post discharge was found to be more cost effective than no post-discharge prophylaxis. |
| Other considerations | None. |

# 36 Bariatric surgery

## 36.1 Introduction

Bariatric or metabolic weight loss surgery is used as a treatment for people who are very obese with a BMI of 40 or greater, or a BMI between 35 and 40 with an obesity-related condition. It can lead to significant weight loss and help improve many obesity-related conditions, such as type 2 diabetes and high blood pressure. Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and its complication, pulmonary embolism (PE), is a common cause of morbidity and mortality after bariatric surgery. There is a need to identify how to reduce this risk of VTE using mechanical or pharmacological prophylaxis.

Although part of gastrointestinal surgery, all patients undergoing bariatric surgery would already be considered at increased risk of VTE because they have a BMI greater than 30 and are therefore classified as obese. Consequently, we have mentioned them separately. Most bariatric surgery is performed laparoscopically.

Factors that may increase the risk of bleeding or the hazard associated with it:

- Difficult access may result in poor views because of obesity
- There is a danger of converting from laparoscopic to open surgery if bleeding occurs.

Other factors that may affect the choice of prophylaxis:

- There may be a higher number of patients who are contraindicated to anti-embolism stockings in this group because of an unusual leg size and shape.

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

For full details see review protocol in appendix C.

**Table 211: PICO characteristics of review question**

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|---|---|
| **Population** | Adults and young people (16 years and older) undergoing bariatric surgery who are admitted to hospital, and outpatients post-discharge |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological (no minimum duration):<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*) |

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

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| | • 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<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

## 36.3 Clinical evidence

**Three studies were included in the review[273,280,149,162]; these are summarised in Table 212 below. Evidence from these studies is summarised in the clinical evidence summary below (Table** 213**,**

**Table 214 and**

Table 215). 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 212: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes |
|---|---|---|---|
| Imberti 2014[149] | Intervention (n=119):<br>LMWH, paraparin, 6400IU once daily (very high dose), subcutaneously administered from 12 hours pre-operatively for 9±2 days. IPCD and AES were worn by 62.2%<br><br>Comparison (n=131):<br>LMWH, paraparin, 4250IU once daily (very high dose), subcutaneously administered from 12 hours pre-operatively for 9±2 days. IPCD and AES were worn by 58%<br><br>Concomitant treatment:<br>Early mobilisation was encouraged and accomplished with 96.4% of patients | n=250<br><br>People undergoing open and laparoscopic primary or revisional bariatric surgery (laparoscopic gastric bypass 68%, laparoscopic sleeve gastrectomy 8.8%, laparoscopic gastric banding 8.4%, biliopancreatic diversion 9.6%, vertical gastroplasty 0.4%)<br><br>BMI (mean ± SD): 44.4<br>Age (mean): 40.9 years<br>Gender (male to female ratio): 1:4<br><br>Italy | All-cause mortality (90 days)<br><br>DVT (symptomatic and asymptomatic) (11 days): confirmed by colour Doppler ultrasound<br><br>PE (11 days): confirmed by perfusion lung scan matched with chest X-ray, ventilation/perfusion scan, computed tomography, angiography<br><br>Heparin-induced thrombocytopaenia (11 days) |
| Kalfarentzos 2001[162] | Intervention (n=30):<br>LMWH, nadroparin, 9500IU, once daily (very high dose) | n=60<br><br>People scheduled to undergo Roux-en-Y gastric bypass | DVT (symptomatic and asymptomatic) (90 days): confirmed by |

| Study | Intervention and comparison | Population | Outcomes |
|---|---|---|---|
| | subcutaneously given from pre-operatively (time-point not reported) until discharge (mean 10.2 days).<br><br>Comparison (n=30):<br>LMWH, nadroparin, 5700IU, once daily (high dose) subcutaneously given from pre-operatively (time-point not reported) until discharge (mean 9.4 days). | surgery<br><br>BMI (mean ± SD): 48.7<br>Age (mean): 35 years<br>Gender (male to female ratio): 1:4<br><br>Greece | Major bleeding (time-point unclear): defined as |
| Steele 2015[280]<br><br>EFFORT trial | Intervention 1 (n=98):<br>LMWH, standard dose pre-op and high dose post-op (enoxaparin 40mg 1x pre-op and 40mg x2 daily post-op). Given until discharge<br><br>Intervention 2 (n=100):<br>Fondaparinux. 5mg once daily post-op. Given until discharge<br><br>Concomitant care:<br>Sequential compression devices and anti-embolic stockings 4-6 hours post-op, early mobilisation | n=198<br><br>People having bariatric surgery (laproscopic vertical sleeve gastrectomy 37.9%; laproscopic Roux-en Y gastric bypass 62.1%)<br><br>BMI (mean ± SD): 45.4±5.4<br>Age (mean): 41.1 years<br>Gender (male to female ratio): 1:5<br><br>USA | DVT (symptomatic and asymptomatic) (14 days): confirmed by magnetic resonance venography<br><br>Thrombocytopaenia (14 days) |

**Table 213: Clinical evidence summary: LMWH (standard dose pre-op, high dose post-op; standard duration) versus fondaparinux**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with fondaparinux | Risk difference with LMWH (standard pre-op, high post-op) (95% CI) |
| DVT (symptomatic and asymptomatic) | 177 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.13 (0.16 to 7.86) | 21 per 1000 | 3 more per 1000 (from 18 fewer to 146 more) |
| Heparin-induced thrombocytopaenia | 177 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 0.15 (0 to 7.73) | 11 per 1000 | 9 fewer per 1000 (from 11 fewer to 66 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 214: Clinical evidence summary: LMWH (very high dose; standard 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 (high dose) | Risk difference with LMWH (very high dose) (95% CI) |
| DVT (symptomatic and asymptomatic) | 60 (1 study) 90 days | VERY LOW[b,c,e] due to risk of bias, indirectness imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000 (from 60 fewer to 60 more)[a] |
| Major bleeding | 60 (1 study) time-point unclear | VERY LOW[b,c,e] due to risk of bias, indirectness, imprecision | OR 7.65 (0.47 to 125.22) | 0 per 1000 | -[d] |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH (high dose) | Risk difference with LMWH (very high dose) (95% CI) |

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.
d Absolute effects could not be calculated due to zero events in one of the arms
e Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

**Table 215: Clinical evidence summary: LMWH (very high dose; standard duration) + IPCD + AES versus LMWH (high dose; standard duration) + IPCD + AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH (high dose) + IPCD + AES | Risk difference with LMWH (very high dose) + IPCD + AES (95% CI) |
| All-cause mortality | 250<br>(1 study)<br>90 days | VERY LOW[b,c]<br>due to indirectness, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[a] |
| DVT (symptomatic and asymptomatic) | 250<br>(1 study)<br>11 days | VERY LOW[b,c]<br>due to indirectness, imprecision | OR 1.1<br>(0.07 to 17.76) | 8 per 1000 | 1 more per 1000<br>(from 7 fewer to 113 more) |
| PE | 250<br>(1 study)<br>11 days | VERY LOW[b,c]<br>due to indirectness, imprecision | OR 0.15<br>(0 to 7.51) | 8 per 1000 | 6 fewer per 1000<br>(from 8 fewer to 47 more) |
| Heparin-induced thrombocytopaenia | 250<br>(1 study)<br>11 days | VERY LOW[b,c]<br>due to indirectness, imprecision | OR 1.1<br>(0.07 to 17.76) | 8 per 1000 | 1 more per 1000<br>(from 7 fewer to 113 more) |

a Zero events in both arms. Risk difference calculated in Review Manager

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with LMWH (high dose) + IPCD + AES | Risk difference with LMWH (very high dose) + 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 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol | | | | | |

## 36.4 Economic evidence

**Published literature**

One health economic study was identified with the relevant comparison and has been included in this review.[305] This is summarised in the health economic evidence profile below (Table 216) and the health economic evidence table in appendix J.

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

**Table 216: Health economic evidence profile: LMWH (standard dose, standard duration) + AES (knee-length) vs LMWH (standard dose, standard duration) + AEs (thigh-length ) vs LMWH (standard dose, standard duration)**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Wade 2015[305] ([UK]) | Partially applicable [(a)] | Potentially serious limitations [(b)] | - **Study type**: CUA using decision modelling<br>- **Population**: Patients undergoing any general surgery (subgroups considered were high risk patients, medium risk patients and low risk patients).<br>- **Interventions:**<br>**Intervention 1:**<br>LMWH (for duration of 7 days (standard duration).<br>**Intervention 2:**<br>Knee-length AES in addition to LMWH for a duration of 7 days (standard duration).<br>**Intervention 3:**<br>Thigh-length AES in addition to pharmacological prophylaxis (LMWH) for duration of 7 days (standard duration). | **High risk patients:**<br>1 (vs 3) : £176<br>2 (vs 3): £177<br>3: comparator | **High risk patients:**<br>1 (vs 3): 0.009 QALYs lost<br>2 (vs 3) : 0.007 QALYs lost<br>3: comparator | **High risk patients:**<br>LMWH + thigh-length AES (intervention 3) dominant (less costly and more effective) | The results of all scenario and sensitivity analyses were largely consistent with the base case analysis for all subgroups |

*Abbreviations: AES: anti-embolism stockings; CUA: cost utility analysis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; QALY: quality-adjusted life years; RCT: randomised controlled trial*

*(a) Mixed population of all surgery types, however subgroup analysis is also presented.*

*(b) The model did not include some relevant health outcomes; e.g. clinically-relevant non-major bleeding , minor bleeding and surgical site infection.*

## 36.5 Evidence statements

**Clinical**

LMWH started pre-operatively at standard dose followed by LMWH at a high dose from post-operatively for standard duration was compared with fondaparinux. The outcomes DVT (symptomatic and asymptomatic) and heparin-induced thrombocytopaenia were reported in one study. There was possible clinical benefit of LMWH in terms of heparin-induced thrombocytopaenia and no clinical difference in terms of DVT (symptomatic and asymptomatic). There was very serious imprecision around both of these results. The quality of the evidence was very low due to risk of bias and imprecision.

LMWH at a very high dose for a standard duration was compared with LMWH at a high dose for a standard duration. The outcomes DVT (symptomatic and asymptomatic) and major bleeding were reported in one study. There was possible clinical harm of LMWH at a very high dose in terms of major bleeding and no clinical difference in terms of DVT (symptomatic and asymptomatic). However there was considerable uncertainty around both of these results. The quality of the evidence was very low due to risk of bias, indirectness and imprecision. The outcomes were downgraded for indirectness as the interventions dose exceeded the maximum dose as highlighted in the evidence review protocol.

LMWH at a very high dose for a standard duration in combination with IPCD and AES was compared with LMWH at a high dose for a standard duration in combination with IPCD and AES. The outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and heparin-induced thrombocytopaenia were reported in one study. There was possible clinical benefit of LMWH at a very high dose in combination with IPCD and AES in terms of PE but no clinical difference for the other outcomes reported in this study. There was considerable uncertainty around these results. The quality of evidence was very low due to indirectness and imprecision. The outcomes were downgraded for indirectness as the interventions dose exceeded the maximum dose as highlighted in the evidence review protocol.

**Economic**

- One cost-utility analysis found that for VTE prophylaxis in high risk general surgery patients, LMWH (standard dose, standard duration) + thigh-length AES was dominant (less costly and more effective) compared to LMWH (standard dose, standard duration) alone. This analysis was assessed as partially applicable with potentially serious limitations

## 36.6 Recommendations and link to evidence

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| **Recommendations** | **1.5.41 Offer VTE prophylaxis to people undergoing bariatric surgery. [2018]**<br><br>**1.5.42 Start mechanical VTE prophylaxis on admission for people undergoing bariatric surgery. Choose either:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression.**<br><br>**Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [2018]**<br><br>**1.5.43 Add pharmacological VTE prophylaxis for people undergoing** |

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| | **bariatric surgery for a minimum of 7 days for people whose risk of VTE outweighs their risk of bleeding. Choose either:**<br>• **LMWH[cc] or**<br>• **fondaparinux sodium[dd]. [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 (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.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Three studies were included in this evidence review. As the very high doses reported in two of the studies exceeded the maximum limit identified in the evidence review protocol the committee decided that the outcome data should be downgraded for indirectness. The committee agreed that this was appropriate (rather than excluding the papers) because due to the nature of the population, evaluations using higher doses may be expected in studies. The committee pointed out that obese people may require higher doses of anticoagulants to achieve the same effect, although there is no clear evidence for this (please refer to Chapter 11 for further discussion). |
| Trade-off between clinical benefits and harms | The committee discussed the evidence presented and noted the poor quality of direct evidence and lack of clinically important effects for this population. The committee agreed that bariatric surgery is a subset of abdominal surgery and therefore the abdominal surgery recommendations would apply in the absence of evidence to the contrary. The committee also noted that people undergoing bariatric surgery would usually be considered at increased risk of VTE because they are all obese.<br>The committee discussed the choices of mechanical prophylaxis and considered that as there was no evidence of superiority of one over the other, it was best to offer clinicians the choice of IPC or anti-embolism stockings. The committee noted that stockings may be difficult to fit for some people who have had bariatric surgery due to the size and shape of the leg. It was also noted by the committee that as there is a higher incidence of diabetes in this population, a number of people may be contraindicated to stockings due to diabetic neuropathy. The committee considered that clinicians should be given the freedom to decide which would be the most appropriate form of mechanical prophylaxis for their individual patient.<br>Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a |

[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), 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.

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| | patient is mobile. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials extrapolated from the abdominal surgery was between 7 and 10 days. |
| Trade-off between net clinical effects and costs | No economic studies were identified to specifically cover bariatric surgery patients; however, one economic study that has been included in the major abdominal surgery review covered the general surgical population stratified according to the risk of VTE. The committee considered that this evidence can be applicable to the bariatric surgery population; specifically the "high risk" subgroup. The study is a cost-utility analysis for standard duration prophylaxis. It was assessed as partially applicable with potentially serious limitations.<br><br>This analysis has shown that combined prophylaxis using LMWH + AES (thigh length) was dominant (more effective and less costly) compared to single prophylaxis with LMWH (standard dose, standard duration) only and combined prophylaxis of LMWH (standard dose, standard duration)+ AES (knee-length). The committee discussed whether the evidence was enough to recommended either knee or thigh length AES. The economic evidence supported the cost effectiveness of combined prophylaxis that includes thigh-length AES, however the committee noted that thigh-length AES are less convenient for people to wear and are more difficult to fit, especially in the bariatric surgery population. Hence the committee agreed that the choice of the length of stocking should be made taking into account the preference of the individual and his/her ability to adhere to wearing them. As stockings may not generally be acceptable or feasible to use for many individuals undertaking bariatric surgery due to the size or shape of the leg, IPCD was also recommended as an alternative option that requires less nursing time in terms of fitting and monitoring.<br><br>The committee also agreed that both LMWH and fondaparinux should be recommended as pharmacological options to address issues of contraindications and individual preferences. |
| Other considerations | The committee noted that the majority of bariatric operations are completed laparoscopically. Less invasive procedures such as laparoscopic procedures are in general associated with a lower risk of VTE than open surgery. However, bariatric surgery may also result in venous compression and stasis due to the pneumoperitoneum and be prolonged.<br><br>The studies identified for this population evaluated different doses of LMWH and presented the necessity to explore the issue of dose-adjustment for LMWH in obese people. The BAFLUX study [150] was not included in this evidence review as it did not reported any relevant outcomes as per protocol. However, this study evaluated the pharmacodynamics associated with using very high dose LMWH compared with a standard dose measuring anti-Xa activity. The study found that a standard dose in morbidly obese patients could be adequate prophylaxis based on this surrogate outcome. However there is no definitive evidence that anti-Xa levels are directly related to DVT/PE outcome.[16] The committee made a recommendation about dose-adjustment taking into account the lack of evidence (see section 11.6). |

# 37 Cardiac surgery

## 37.1 Introduction

This section covers patients undergoing cardiac surgery.

Factors that may alter the risk of VTE in cardiac surgery:

- Pacing wires and implantable cardioverter-defibrillator devices may lead to an increase in upper limb deep vein thrombosis

Factors that increase the risk of bleeding or hazard associated with it:

- Many patients will be receiving antiplatelet medication, heparin or warfarin and will therefore have an increased risk of bleeding.

Other special factors that would affect the choice of, and use of, specific methods of prophylaxis:

- Several procedures in cardiac surgery involve the use of anticoagulation or antiplatelet therapy:
  - Full heparin anticoagulation is used during cardiopulmonary bypass which is typically 1-2 hours of a 2-5 hour surgery.
  - Surgeries performed "off pump" (without the use of heart lung machines) are also covered by heparin anticoagulation.
  - Most patients with coronary artery disease are given antiplatelet therapy up to shortly prior to surgery and it is recommenced soon after.
  - Many patients with valve disease have warfarin anticoagulation.
  - Patients in atrial fibrillation will generally have warfarin or other anticoagulants.
- Many cardiac surgery patients have leg veins removed for use as grafts. This would preclude the use of both AES and IPCD during the surgery but they could be used afterwards.

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

For full details see the review protocol in appendix C.

**Table 217: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) undergoing cardiac surgery who are:<br>• Admitted to hospital<br>• Discharged from hospital<br>• Outpatients |
| **Interventions** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously) |

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| | • Low molecular weight heparin (LMWH), licensed in UK:<br>  ○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60mg twice daily*)<br>  ○ 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*)<br>  ○ 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*)<br>• LMWH, licensed in countries other than UK:<br>  ○ bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>  ○ certoparin (3000 units daily)<br>  ○ nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>  ○ parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>  ○ reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>  ○ warfarin (variable dose only)<br>  ○ acenocoumarol (all doses)<br>  ○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300 mg)*<br><br>*off-label |
| **Comparisons** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | **Critical outcomes:**<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br><br>**Important outcomes:**<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Major adverse cardiac events (MACE) (duration of study): death, Q-wave myocardial infarction (MI) and the need for repeat revascularization by redo-CABG or repeat percutaneous intervention |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs |

## 37.3 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of mechanical and pharmacological prophylaxis strategies (alone or in combination) in people undergoing cardiac surgery. Two new studies were identified (Kolluri 2016[171]; Myles 2016[222]). Of the three studies included in the previous guideline (CG92), one study was included[116,249], and two studies were excluded (Beghi 1993[18]; Ramos 1996[249]). The included study is summarised in Table 218 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.

**Summary of included studies**

**Table 218: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Goldhaber 1995[116] | Intervention (n = 172)<br>Thigh-length IPCD<br>+ AES (unknown length)<br>+ aspirin 325 mg/day.<br>Started post-operatively<br><br>Comparison ( n=172)<br>AES (unknown length)<br>+ aspirin 325 mg/day.<br>Started post-operatively | n=344<br><br>People having coronary artery bypass<br><br>Adults (mean age 63.2±9.7 years)<br><br>Male to female ratio 229:112<br><br>USA | All-cause mortality (until discharge)<br><br>DVT (≥4 days post-op until discharge): confirmed by bilateral Doppler ultrasound<br><br>PE (until discharge): confirmed by high probability V/Q scan<br><br>Fatal PE: confirmed by: assumed clinical evaluation (pulmonary emobolectomy procedure) | First 98 patients enrolled had delayed initiation of prophylaxis with IPCD<br><br>Significantly greater proportion of people in the comparison group had cancer (numbers not reported in CG92) |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Kolluri 2016[171] | Intervention (n = 41)<br>Fondapainux (2.5mg subcutaneously, once daily) starting at a mean of 12 hours after wound closure or in the morning of the first postoperative day. Administered for 9 days or until discharge.<br><br>Comparison ( n=37)<br>No VTE prophylaxis (subcutaneous injections of saline)<br><br>Both groups routinely received AES and/or IPCD | n=78<br><br>People having coronary artery bypass graft surgery<br><br>Adults (mean age: intervention 64.4±8.9; comparison 62±8.9)<br><br>Male to female ratio 57:21<br><br>USA | DVT (9-11 days): confirmed by duplex ultrasound | |
| Myles 2016[222] | Intervention (n=1059):<br>Aspirin (100mg) starting 1-2 hours before surgery, with or without anxiolytic premedication<br><br>Comparison (n=1068):<br>No VTE prophylaxis (matched placebo tablets 1 to 2 hours before surgery, with or without anxiolytic premedication) | n=2127<br><br>People having coronary artery surgery who are at increased risk for complications<br><br>Adults (mean age: intervention 66.5±9.7; comparison 66.2±10.2)<br><br>Male to female ratio 1730:370<br><br>Australia | All-cause mortality (30 days)<br><br>PE (30 days): method of confirmation not reported<br><br>Major bleeding (30 days): defined as any excessive bleeding leading to surgical re-exploration | There was no limitation to the use or postoperative aspirin or other antiplatelet therapy, and such therapy was administered in accordance with local practices |

**Table 219: Clinical evidence summary: IPC + AES + aspirin compared to AES + aspirin**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with AES + aspirin | Risk difference with IPCD + AES + aspirin (95% CI) |
| All-cause mortality | 330 (1 study) until discharge | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 7.53 (0.47 to 120.83) | 0 per 1000 | Not estimable[a] |
| DVT | 330 (1 study) ≥4 days post-op until discharge | VERY LOW[b,c] due to risk of bias, imprecision | RR 0.87 (0.57 to 1.34) | 217 per 1000 | 28 fewer per 1000 (from 93 fewer to 74 more) |
| PE | 330 (1 study) until discharge | VERY LOW[b,c] due to risk of bias, imprecision | RR 1.01 (0.06 to 16.05) | 6 per 1000 | 0 more per 1000 (from 6 fewer to 91 more) |
| PE, fatal | 329 (1 study) until discharge | VERY LOW[b,c] due to risk of bias, imprecision | Peto OR 1.01 (0.06 to 16.15) | 6 per 1000 | 0 more per 1000 (from 6 fewer to 84 more) |

a Zero events in control arm
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 220: Clinical evidence summary: Aspirin versus no 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 Aspirin versus no prophylaxis (95% CI) |
| All-cause mortality | 2100 (1 study) | LOW[a] due to | RR 1.56 (0.68 to 3.6) | 9 per 1000 | 5 more per 1000 (from 3 fewer to 22 more) |

| 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 Aspirin versus no prophylaxis (95% CI) |
| | 30 days | imprecision | | | |
| PE | 2100<br>(1 study)<br>30 days | LOW[a]<br>due to imprecision | RR 0.8<br>(0.32 to 2.03) | 9 per 1000 | 2 fewer per 1000<br>(from 7 fewer to 10 more) |
| Major bleeding | 2100<br>(1 study)<br>30 days | LOW[a]<br>due to imprecision | RR 0.87<br>(0.47 to 1.6) | 21 per 1000 | 3 fewer per 1000<br>(from 11 fewer to 13 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 221: Clinical evidence summary: Fondaparinux + AES and/or IPCD versus AES and/or IPCD for VTE prophylaxis in people undergoing cardiac surgery**

| 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 Fonda + AES/IPCD versus AES/IPCD (95% CI) |
| DVT | 67<br>(1 study)<br>9-11 days | LOW[a]<br>due to imprecision | Peto OR 0.12<br>(0 to 6.23) | 31 per 1000 | 27 fewer per 1000<br>(from 31 fewer to 136 more) |
| a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs | | | | | |

## 37.4 Economic evidence

**Published literature**

No relevant health economic studies were identified.

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

## 37.5 Evidence statements

**Clinical**

In one study of very low quality, a possible clinical benefit of IPCD + AES + aspirin was found for the outcome all-cause mortality, however there was very serious imprecision around the estimate, and therefore was also associated with no difference and clinical harm (n=330). For the DVT outcome, evidence from the same study showed a possible clinical harm of IPCD + AES + aspirin, however again there was very serious imprecision around the estimate. There was no clinical difference between the two interventions in terms of PE or fatal PE. The evidence for these outcomes also showed very serious imprecision and was associated with both clinical benefit and clinical harm.

One study compared aspirin to no VTE prophylaxis. There was a possible clinical harm of aspirin compared to no prophylaxis in terms of all-cause mortality, and no clinical difference between the two interventions for the PE and major bleeding outcomes (low quality; n=2100). For all outcomes there was very serious imprecision around the estimate.

One small study of 67 participants compared a combination of fondaparinux and mechanical prophylaxis with mechanical prophylaxis alone. The evidence demonstrated a possible clinical benefit for combined fondaparinux and mechanical prophylaxis in terms of DVT, however there was very serious imprecision around the estimate and therefore was also associated with no difference or clinical harm. No other outcomes were reported.

**Economic**

- No relevant economic evaluations were identified.

## 37.6 Recommendations and link to evidence

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| **Recommendations** | **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:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression.**<br><br>**Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [2018]**<br><br>**1.5.45 Consider adding pharmacological VTE prophylaxis for a minimum of 7 days for people who are undergoing cardiac surgery and are not** |

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| | **having other anticoagulation therapy:**<br>• **Use LMWH[ee] as first-line treatment.**<br>• **If LMWH[ff] is contraindicated use fondaparinux sodium[gg]. [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 (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.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br>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 committee noted that there was little RCT evidence covering cardiac surgery. The included studies were generally well conducted methodologically with down-grading occurring predominantly due to imprecision. |
| Trade-off between clinical benefits and harms | The key risks in this patient group are risk of bleeding as they are likely to already be receiving antiplatelet medication. Additionally, this patient group has a high average age, and are likely to have undergone a long operation and a period of immobilisation.<br>Cardiac surgery patients receive a large dose of heparin/anticoagulant during the surgery at the time of clamping, so any pharmacological VTE prophylaxis would not be initiated until after surgery.<br>The committee noted the relatively small amount of evidence in this particular population. The committee pre-specified that if this was the case they would consider the evidence for the abdominal surgery population as indirect evidence. Both cardiac and abdominal surgery involves operations potentially lasting several hours and significant potential for post-operative immobility partly due to the presence of a large incision. The committee discussed the current evidence, considered the previous CG92 recommendations for the cardiac surgery population, as well as the recommendations for the abdominal surgery population. The committee considered that similar pharmacological VTE prophylaxis recommendations could be made for this population as for abdominal surgery patients (LMWH and fondaparinux). The committee considered that the small amount of evidence for fondaparinux identified in the cardiac population suggested a benefit for reducing DVT and that this was a reasonable addition to the |

[ee] 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.

[ff] 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.

[gg] 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.

| | |
|---|---|
| | recommended options from CG92. However, the use of fondaparinux sodium in the cardiac surgery population is off-label as fondaparinux sodium did not have a UK marketing authorisation for this indication at the time of consultation (October 2017). Therefore the committee recommend LMWH in the first instance and fondaparinux sodium only if LMWH is contraindicated.<br><br>Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a patient is mobile. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials extrapolated from the abdominal surgery was between 7 and 10 days. |
| Trade-off between net clinical effects and costs | No economic studies were identified for this review. Unit costs were presented.<br><br>The committee highlighted that the VTE risk in people undergoing cardiac surgery is high. They discussed that current practice follows the recommendation of CG92, where combined prophylaxis (pharmacological and mechanical) was considered to be cost effective for this population. The clinical evidence presented limited their ability to draw a conclusion specific for this population and that extrapolation from the abdominal surgery population for which combined prophylaxis was recommended would be acceptable. Given the high baseline risk of VTE in this population, it was considered that the additional cost of combined prophylaxis would be off-set by the savings from the averted VTE events. The choice of the mechanical and pharmacological prophylaxis options was considered. It was determined that the options given for the abdominal surgery population should be recommended for the cardiac surgery population to allow for tailored prophylaxis prescribing, accommodating licence restrictions, the presence of contraindications and patient preferences. |
| Other considerations | The committee noted that current practice is to use AES as opposed to graduated compression stockings. In terms of pharmacological prophylaxis, current practice is to give a large dose of heparin pre-operatively which is then reversed post-operatively and a lower dose is then offered. Therefore there is a different risk of VTE in these two distinct stages. |

# 38 Thoracic surgery

## 38.1 Introduction

Thoracic surgery involves the repair of organs located in the thorax, or chest. Factors that may alter the risk of VTE in people undergoing thoracic surgery:

- After lung resection, pulmonary embolism to the remaining lung carries a commensurately higher risk of death.
- Most patients who have video-assisted thorascopic surgery (VATS), particularly for pneumothorax, are young (less than 30 years) and are able to walk around the ward up to the time of surgery and soon after and have short lengths of stay.

There are no special factors that increase the risk of bleeding or the hazard associated with it in thoracic surgery. There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in thoracic surgery.

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

For full details see review protocol in appendix C.

**Table 222: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) undergoing thoracic surgery who are admitted to hospital, and outpatients post-discharge |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (AES (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological (no minimum duration):<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ 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*)<br>○ 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*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ 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)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists: warfarin (variable dose), acenocoumarol (all doses), phenindione (all doses)<br>• Fondaparinux (all doses)<br>• Apixaban (all doses)<br>• Dabigatran (all doses)<br>• Rivaroxaban (all doses)<br>• Aspirin (up to 300mg)*<br><br>*off-licence |
| **Comparison(s)** | • Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo) |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge) (NMA outcome)<br>• Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) (NMA outcome)<br>• Pulmonary embolism (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE (NMA outcome)<br>• Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (NMA outcome)<br>• 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<br><br>Important outcomes:<br>• 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<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs |

## 38.3 Clinical evidence

No relevant clinical studies comparing different pharmacological and mechanical prophylaxis strategies for people undergoing thoracic surgery were identified. Papers included in the previous guideline (CG92) in the major surgery review were considered for inclusion in addition to papers identified in the update.

## 38.4 Economic evidence

**Published literature**

One health economic study was identified with the relevant comparison and has been included in this review.[305] This is summarised in the health economic evidence profile below (Table 223) and the health economic evidence tables in appendix J.

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

**Table 223: Health economic evidence profile: LMWH (standard dose, standard duration) + AES (knee-length) vs LMWH (standard dose , standard duration) + AEs (thigh-length ) vs LMWH (standard dose, standard duration)**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Wade 2015[305] ([UK]) | Partially applicable [(a)] | Potentially serious limitations [(b)] | - **Study type**: CUA using decision modelling<br>- **Population**: Patients undergoing any general surgery (subgroups considered were high risk patients, medium risk patients and low risk patients).<br>- **Interventions:**<br>**Intervention 1:**<br>LMWH (for duration of 7 days (standard duration).<br>**Intervention 2:**<br>Knee-length AES in addition to LMWH for a duration of 7 days (standard duration).<br>**Intervention 3:**<br>Thigh-length AES in addition to pharmacological prophylaxis (LMWH) for duration of 7 days (standard duration). | **High risk patients:**<br>1 (vs 3) : £176<br>2 (vs 3): £177<br>3: comparator | **High risk patients:**<br>1 (vs 3): 0.009 QALYs lost<br>2 (vs 3) : 0.007 QALYs lost<br>3: comparator | **High risk patients:**<br>LMWH + thigh-length AES (intervention 3) dominant (less costly and more effective) | The results of all scenario and sensitivity analyses were largely consistent with the base case analysis for all subgroups |

*Abbreviations: AES: anti-embolism stockings; CUA: cost utility analysis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; QALY: quality-adjusted life years; RCT: randomised controlled trial*

*(c) Mixed population of all surgery types, however subgroup analysis is also presented.*

*(d) The model did not include some relevant health outcomes; e.g. clinically-relevant non-major bleeding , minor bleeding and surgical site infection.*

## 38.5 Evidence statements

### Clinical

No relevant clinical studies were identified.

### Economic

- One cost-utility analysis found that for VTE prophylaxis in high risk general surgery patients, LMWH (standard dose, standard duration) + thigh-length AES was dominant (less costly and more effective) compared to LMWH (standard dose, standard duration) alone and to LMWH (standard dose, standard duration)+ AES (knee-length). This analysis was assessed as partially applicable with potentially serious limitations.

## 38.6 Recommendations and link to evidence

| | |
|---|---|
| **Recommendations** | **1.5.46 Consider VTE prophylaxis for people undergoing thoracic surgery who are at increased risk of VTE. [2018]**<br><br>**1.5.47 Start mechanical VTE prophylaxis on admission for people undergoing thoracic surgery. Choose either:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression.**<br>**Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [2018]**<br><br>**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:**<br>• **Use LMWH[hh] as first-line treatment.**<br>• **If LMWH[ii] is contraindicated use fondaparinux sodium[jj]. [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 |

[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), 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.

[jj] At the time of publication (March 2018), fondaparinux sodium 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.

| | |
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| | hospital discharge) as critical outcomes.<br>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 thrombocytopaenia (duration of study) and technical complications of mechanical interventions (duration of study) as important outcomes.<br>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 clinical evidence was identified for this review. |
| Trade-off between clinical benefits and harms | In the previous guideline this group was considered together with other major abdominal surgery (gastrointestinal, bariatric, gynaecological, urological). For the update the committee wished to explore if there was any evidence specifically for the thoracic surgery population because it was considered to be different clinically to the abdominal surgery population both in terms of the procedures involved and the fact that the chest and not the abdomen or pelvis that was being operated on. In the absence of direct evidence the committee considered it would be reasonable to extrapolate the recommendations from the abdominal surgery population to this population, including the strength of the recommendation as this is a high risk group. However the use of fondaparinux sodium in the thoracic surgery population is off-label as fondaparinux sodium did not have a UK marketing authorisation for this indication at the time of consultation (October 2017). Therefore the committee recommend LMWH in the first instance and fondaparinux sodium only if LMWH is contraindicated.<br>Following lung resection, the risk of PE in the remaining lung is higher. Some patients having certain types of thoracic surgery (for example video-assisted thorascopic surgery) are younger, are mobile up to the time of surgery and soon after.<br>Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a patient is mobile. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials extrapolated from the abdominal surgery was between 7 and 10 days. |
| Trade-off between net clinical effects and costs | No economic studies were identified to specifically cover thoracic surgery patients; however, one economic study that has been included in the major abdominal surgery review covered the general surgical population stratified according to the risk of VTE. The committee considered that this evidence can be applicable to the thoracic surgery population, specifically the “high risk” subgroup. The study is a cost-utility analysis for standard duration prophylaxis. It was assessed as partially applicable with potentially serious limitations.<br>This analysis showed that combined prophylaxis using LMWH + AES (thigh length) was dominant (more effective and less costly) compared to single prophylaxis with LMWH only (standard dose, standard duration) only and combined prophylaxis of LMWH (standard dose, standard duration)+ AES (knee-length). The committee discussed whether the evidence was enough to recommended either knee or thigh length AES. The economic evidence supported the cost effectiveness of combined prophylaxis that includes thigh-length AES, however the committee noted that thigh-length AES are less convenient for people to wear and are more difficult to fit. Hence, the committee agreed that the choice of the length of stocking should be made taking into account the preference of the individual and his/her ability to adhere to wearing them. IPCD was also recommended as an alternative option that requires less nursing time in terms of fitting and monitoring.<br>The committee also agreed that both LMWH and fondaparinux should be recommended as pharmacological options to address issues of contraindications and individual preferences. As fondaparinux use in this population is off-licence it should |

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| | only be considered where LMWH is contraindicated. |
| Other considerations | The 'consider' recommendation is a reflection of the lack of evidence in this population. However, it is the committee's view that for this group of patients, prophylaxis is likely to be most clinically and cost effective for those assessed to be at high risk of VTE. |

# 39 Vascular surgery

## 39.1 Introduction

This section covers patients undergoing vascular surgery. Vascular surgery is a surgical specialty dealing specifically with disorders of the arteries, veins and lymphatics around the body excluding the heart and brain. It also includes dealing with the consequences of vascular disease, such as limb amputation. Procedures range from these which can be long and involve interruption of flow in vessels and reduce patient mobility, to those which are more minor and can be done as day cases such as varicose veins surgery. High doses of anticoagulation are often given as part of the surgical procedure on more major cases.

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and its complication, pulmonary embolism (PE), is a common cause of morbidity and mortality after vascular surgery unless prophylaxis is given. However there are often also high risks of bleeding. There is a need to identify how to best reduce this risk of VTE using mechanical or pharmacological prophylaxis.

Factors that may alter the risk of VTE:

- Arterial surgery patients are often elderly and immobile.
- Many arterial surgery patients will already be receiving antiplatelet therapy and some will be on warfarin or other anticoagulants.
- Systemic heparin is frequently administered during surgery for arterial disease.
- Surgery for varicose veins is mostly in women; oral contraceptive use and hormone replacement therapy are therefore more commonly associated with varicose veins surgery.

Factors that increase the risk of bleeding or hazard associated with it:

- Patients using anticoagulation or antiplatelet therapy not related to surgery will have an increased risk of bleeding.

Other factors that may alter the choice of prophylaxis:

- The use of intermittent compression devices is contraindicated in patients with peripheral arterial disease.
- The use of intermittent compression devices and anti-embolism/graduated compression stockings will usually be inappropriate on the operated leg for a patient undergoing lower limb arterial surgery.
- Anti-embolism/graduated compression stockings will be contraindicated for patients with lower limb arterial disease.

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

**Table 224: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) undergoing vascular surgery who are admitted to and discharged from hospital |
| **Interventions** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID) |

| | |
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| | • Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>  ○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>  ○ 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*)<br>  ○ 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*)<br>• LMWH, licensed in countries other than UK:<br>  ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>  ○ Certoparin (3000 units daily)<br>  ○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>  ○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>  ○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>  ○ warfarin (variable dose only)<br>  ○ acenocoumarol (all doses)<br>  ○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300mg)*<br><br>*off-label |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis.<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• Pulmonary embolism (symptomatic and asymptomatic) (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<br>• 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<br>• 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<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |
| **Strata** | Open vascular surgery (major aortic/leg bypass)<br>Varicose veins<br>Lower limb amputation |

## 39.3 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of mechanical and pharmacological prophylaxis strategies (alone or in combination) in people undergoing vascular surgery.

Eight RCTs reporting at least one of the three main outcomes were identified. Four studies were identified from the search[13 ,265 ,306 ,325] and five studies were included from the previous guideline CG92[20 ,91 190 ,275]. One of the studies included in CG92 was excluded (Killewich 1997[164]) as the length of follow up does not match the review protocol. Of the studies included from CG92, data for two studies [20 ,275] were extracted from a systematic review[61]. Evidence from all the studies is summarised in the clinical evidence summary below (Table 225). See also the study selection flow chart in appendix E, forest plots in Appendix L, study evidence tables in appendix H (details of the systematic review are also reported in appendix H), GRADE tables in appendix K and excluded studies list in appendix N.

**Table 225: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| **Strata: overall (not specified)** | | | | |
| Belch 1980[20] | Intervention (n = 24):<br>UFH, 2,500UI pre-operatively then 5,000UI 2x daily for 7 days, administered subcutaneously | n=49<br><br>People undergoing elective aortic bifurcation graft surgery | DVT (timepoint not reported): confirmed by radiolabelled fibrinogen or scanning | The trial was terminated because of excess bleeding complications in patients receiving subcutaneous |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison (n= 25)<br>Placebo, saline injections<br><br>Concomitant treatment:<br>All people received a routine dose of intravenous sodium heparin intra-operatively. | UK<br><br>No further details reported | PE (timepoint not reported): no definition reported<br><br>Major bleeding (timepoint not reported): no definition reported | heparin<br><br>Data extracted from systematic review (Collins 1988 [61]) |
| Farkas 1993[91] | Intervention (n = 122):<br>LMWH (Enoxaparin), 2100IU pre-op (standard dose), 4200IU post-op (high dose). Timing: Begun day pre-op and repeatedly daily until 7th day post- op<br><br>Comparison (n=111):<br>UFH 5000UI pre-op, 7500UI post-op. Timing: Begun day pre-op and repeated twice daily until 7th day post-op<br><br>Concomitant treatment: Intraoperative use of UFH (94.4%) or protamine (7.9%) was authorised in both groups | n=223<br><br>People undergoing vascular surgery (aortic or aortoiliac and aneurysmectomy; aorto- femoral bypass for atherosclerotic disease; and femoropopliteal or femorodistal bypass)<br><br>Adults (mean age intervention 65±11 years, comparison 64±11 years)<br><br>Male to female ratio 200:43 | All-cause mortality (timepoint not reported)<br><br>DVT (10 days): confirmed by Duplex US, confirmed by venography<br><br>PE (timepoint not reported): confirmed by clinical suspicion investigated by angiogram<br><br>Thrombocytopaenia (timepoint not reported) | Numbers in each group for baseline data do not tally with text |
| Spebar 1981[275] | Intervention (n =24):<br>UFH (no further details reported)<br><br>Comparison (n=19):<br>No VTE prophylaxis | n=43<br><br>People undergoing peripheral vascular surgical procedures (including aortic reconstruction n=9, carotid artery reconstruction n=19, lumbar sympathectomy n=3, leg revascularisation n=4, psuedoaneurysm repair n=3, repair of artiovenous fistula n=2) | DVT (timepoint not reported): indicated by iodine-125 fibrinogen scanning<br><br>PE (timepoint not reported): no definition reported<br><br>Major bleeding (timepoint not reported): no definition reported | Data extracted from systematic review (Collins 1988 [61]) |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | No further details reported | | |
| **Strata: limb amputation** | | | | |
| Lastoria 2006[190] | Intervention (n=41): LMWH (enoxaparin), 40mg 1x daily (standard dose). Timing: 12 hours before surgery or in emergency cases in the first postoperative day, until discharge.<br><br>Comparison (n=34): UFH, 5000IU administered subcutaneously. Timing: 12 hours before surgery or in emergency cases in the first postoperative day, until discharge. | n=75<br><br>People undergoing elective or emergency lower-limb amputation (n=30 above-knee; n=45 below-knee)<br><br>Adults (age range 18 to 86)<br><br>Male to female ratio 59:16 | DVT (5-8 days after surgery): confirmed by duplex scanning<br><br>Major bleeding (timepoint not reported): any 'bleeding complications' | Strata: lower limb amputation |
| **Strata: varicose veins** | | | | |
| Ayo 2017 [13] | Intervention (n = 39): AES (thigh high (30-40mmHg) for 24 hours post procedure and then daily during waking hours for 7 days)<br><br>Comparison (n = 46): Usual care, 24 hours of post-procedural bandages (no compression therapy) | n=85<br><br>People undergoing endovenous radiofrequency or laser ablation of great saphenous vein for valvular incompetence<br><br>USA<br><br>Mean age (SD not reported): compression: 52; usual care 49 years<br><br>Male to female ratio 20:65 | QOL: Venous clinical severity score (VCSS) at 7 days<br><br>QOL: Chronic venous insufficiency questionnaire (CIVIQ-2) at 90 days | Strata: varicose vein surgery<br><br>Some people were included in the study twice if they required bilateral treatment (number of people = 70, number of cases = 85) |
| San Norberto Garcia 2013[265] | Intervention (n=132): LMWH (Bemiparin, not UK licensed), 2500/3500IU 1x daily. Started 6 hours after wound closure, continued for 10 days +IPCD for first 7 days + AES (thigh length) + early mobilisation | n=264<br><br>People undergoing elective varicose vein surgery with moderate VTE risk (defined as having 2 risk factors for VTE)<br><br>Adults (mean 67; | DVT (90 days): confirmed by duplex ultrasound<br><br>PE (90 days): confirmed by duplex ultrasound<br><br>Major bleeding (90 days): fatal bleeding, | Strata: varicose vein surgery<br><br>Included people with moderate VTE risk (defined as having 2 risk factors for VTE); excluded people with high risk of |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison (n=130)<br>IPCD for first 7 days then AES (thigh length)<br>+ early mobilisation | range 18-75)<br><br>Male to female ratio 104:162<br><br>Spain | was into a critical organ (e.g. retropeitoneal, intracranial, intraocular, intraspinal), required reoperation, or was clinically over extrasurgical-site bleeding associated with a fall in haemoglobin of ≥20g/L, calculated from preoperated baseline value, or requiring infusion of ≥2U of whole blood or packed cells | bleeding |
| Wang 2015[306] | Intervention 1 (n=531):<br>UFH, 125U/kg, administered subcutaneously for 3 days<br><br>Intervention 2(n=550):<br>LMWH (Enoxaparin), 4000 IU, 1x daily (high dose) for 3 days<br><br>Comparison (n=542)<br>No VTE prophylaxis | n=1623<br><br>People undergoing varicose vein surgery (high ligation and stripping of the GSV, and removal of superficial varicosities)<br><br>Adults (mean age 47.62±10.37; range 23-68 years)<br><br>Male to female ratio: intervention 1 - 1:1.01;<br>2 – 1: 1.04;<br>3 – 1.09 : 1<br><br>China | DVT, proximal (30 days): confirmed by ultrasound<br><br>PE (30 days): computed tomography pulmonary angiography scan<br><br>Major bleeding (30 days): haemorrhage followed by discontinuation of anticoagulation therapy | Strata: varicose vein surgery |
| Ye 2016 [325] | Intervention (n = 200):<br>AES. Elastic bandage placed after the procedure and left in position during the first night. Patients then wore a thigh-high AES (class II, ankle pressure of 23-32 mmHg), during the daytime for at least 2 weeks.<br><br>Comparison (n = 200):<br>Elastic bandage placed | n=400<br><br>People undergoing endovenous ablation for primary unilateral great saphenous vein incompetence<br><br>China<br><br>Age, median (IQR):<br>Compression group 48 (37-59); usual care | All-cause mortality (14 days)<br><br>DVT (14 days): confirmed by ultrasound duplex<br><br>PE (14 days): definition not reported<br><br>QOL: Aberdeen Varicose Vein | Strata: varicose vein surgery |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | after the procedure and left in position during the first night (as in the intervention group). Then AES were not recommended | 49 (40-60)<br><br>Male to female ratio 165:235 | Symptom Severity Score (AVVSS) (28 days) | |

### 39.3.1 Strata: overall (not specified)

**Table 226: Clinical evidence summary: UFH compared to 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) |
| DVT | 92 (2 studies) not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 0.57 (0.22 to 1.46) | 227 per 1000 | 98 fewer per 1000 (from 177 fewer to 105 more) |
| PE | 43 (1 study) not reported | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000 (from 0 fewer to 0 more)[d] |
| Major bleeding | 92 (2 studies) not reported | VERY LOW[a,c] due to risk of bias, indirectness, imprecision | RR 8.33 (1.13 to 61.7) | 23 per 1000 | 167 more per 1000 (from 3 more to 1000 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
d Zero events in both arms. Risk difference calculated in Review Manager

**Table 227: Clinical evidence summary: LMWH (standard dose pre-op/high dose post-op) compared to 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 | 233 | | RR 4.55 | 0 per 1000 | - |

| 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) |
| | (1 study)<br>not reported | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | (0.22 to 93.81) | | |
| DVT | 233<br>(1 study)<br>10 days | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | RR 2.27<br>(0.73 to 7.05) | 36 per 1000 | 46 more per 1000<br>(from 10 fewer to 218 more) |
| PE | 233<br>(1 study)<br>not reported | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | Not estimable[d] | Not estimable[d] | 0 fewer per 1000<br>(from 20 fewer to 20 more)[d] |
| Thrombocytopaenia | 233<br>(1 study)<br>not reported | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | Peto OR 6.81<br>(0.42 to 109.84) | 0 per 1000 | - |

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

### 39.3.2 Strata: Varicose veins

**Table 228: Clinical evidence summary: LMWH +AES + IPCD + mobilisation versus IPCD/AES + mobilisation**

| Outcomes | No of | Quality of the evidence | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | (GRADE) | effect (95% CI) | Risk with IPCD/AES + mobilisation | Risk difference with LMWH +AES + IPCD mobilisation (95% CI) |
|---|---|---|---|---|---|
| DVT | 262 (1 study) 90 days | VERY LOW[b,c] due to risk of bias, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000 (from 10 fewer to 10 more)[a] |
| PE | 262 (1 study) 90 days | VERY LOW[b,c] due to risk of bias, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000 (from 10 fewer to 10 more)[a] |
| Major bleeding | 262 (1 study) 90 days | VERY LOW[b,c] due to risk of bias, imprecision | Not estimable[a] | Not estimable[a] | 0 fewer per 1000 (from 10 fewer to 10 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 229: Clinical evidence summary: LMWH (high dose) 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) |
| DVT | 1092 (1 study) 30 days | HIGH | RR 0.07 (0.02 to 0.29) | 52 per 1000 | 48 fewer per 1000 (from 37 fewer to 51 fewer) |
| PE | 1092 (1 study) 30 days | HIGH | Peto OR 0.13 (0.03 to 0.53) | 15 per 1000 | 13 fewer per 1000 (from 7 fewer to 14 fewer) |
| Major bleeding | 1092 | | Peto OR 0.99 | 2 per 1000 | 0 fewer 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 (high dose) (95% CI) |
| | (1 study)<br>30 days | VERY LOW[a,b]<br>due to indirectness, imprecision | (0.06 to 15.78) | | (from 2 fewer to 26 more) |

a Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

**Table 230: 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) |
| DVT | 1073<br>(1 study)<br>30 days | HIGH | RR 0.11<br>(0.03 to 0.36) | 52 per 1000 | 46 fewer per 1000<br>(from 33 fewer to 50 fewer) |
| PE | 1073<br>(1 study)<br>30 days | HIGH | Peto OR 0.14<br>(0.03 to 0.55) | 15 per 1000 | 13 fewer per 1000<br>(from 7 fewer to 14 fewer) |
| Major bleeding | 1073<br>(1 study)<br>30 days | VERY LOW[a,b]<br>due to indirectness, imprecision | Peto OR 0.14<br>(0 to 6.96) | 2 per 1000 | 2 fewer per 1000<br>(from 2 fewer to 11 more) |

a Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

**Table 231: Clinical evidence summary: LMWH (high dose) 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 (high dose) (95% CI) |
| DVT | 1081<br>(1 study)<br>30 days | LOW[a]<br>due to imprecision | RR 0.64<br>(0.11 to 3.84) | 6 per 1000 | 2 fewer per 1000<br>(from 5 fewer to 16 more) |
| PE | 1081<br>(1 study)<br>30 days | LOW[a]<br>due to imprecision | Not estimable[b] | Not estimable[b] | 0 fewer per 1000<br>(from 0 fewer to 0 more)[b] |
| Major bleeding | 1081<br>(1 study)<br>30 days | VERY LOW[a,c]<br>due to indirectness, imprecision | Peto OR 0.29<br>(0.05 to 1.68) | 8 per 1000 | 5 fewer per 1000<br>(from 7 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
b Zero events in both arms. Risk difference calculated in Review Manager
c Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

**Table 232: Clinical evidence summary: AES versus usual care**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Usual care | Risk difference with Varicose vein strata - AES (95% CI) |
| All-cause mortality | 400<br>(1 study)<br>2 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable | Moderate | |
| | | | | 0 per 1000 | 0 fewer per 1000<br>(from 10 fewer to 10 more)[a] |
| DVT<br>ultrasound duplex | 400<br>(1 study)<br>2 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | Not estimable | Moderate | |
| | | | | 0 per 1000 | 0 fewer per 1000<br>(from 10 fewer to 10 more)[a] |
| Symptomatic pulmonary | 400 | | Not estimable | Moderate | |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Usual care | Risk difference with Varicose vein strata - AES (95% CI) |
| embolism | (1 study)<br>2 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | | 0 per 1000 | 0 fewer per 1000<br>(from 10 fewer to 10 more)[a] |
| HRQOL (AVVSS)<br>Aberdeen Varicose Vein Symptoms Severity Score. Scale from: 0 to 100.<br>Better=lower | 400<br>(1 study)<br>4 weeks | MODERATE[b]<br>due to risk of bias | | The mean HRQOL (AVVSS) in the control groups was 8 | The mean HRQOL (AVVSS) in the intervention groups was<br>0.5 higher<br>(0.19 lower to 1.19 higher) |
| HRQOL (VCSS)<br>Venous clinical severity score. Scale from: 0 to 30.<br>Better=lower | 85<br>(1 study)<br>7 days | VERY LOW[b,c,d]<br>due to risk of bias, indirectness, imprecision | | The mean HRQOL (VCSS) in the control groups was 4.35 | The mean HRQOL (VCSS) in the intervention groups was<br>1.23 lower<br>(4.72 lower to 2.26 higher) |
| HRQOL (CIVIQ-2)<br>Chronic venous insufficiency questionnaire. Scale from: 0 to 100.<br>Better=lower | 85<br>(1 study)<br>90 days | VERY LOW[b,c,d]<br>due to risk of bias, indirectness, imprecision | | The mean HRQOL (CIVIQ-2) in the control groups was 22.5 | The mean HRQOL (CIVIQ-2) in the intervention groups was<br>6.6 higher<br>(7.67 lower to 20.87 higher) |

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 Some people were included in the study twice if they required bilateral treatment (number of people = 70, number of cases = 85)
d Unable to calculate as standard deviations not reported

### 39.3.3 Strata: Lower limb amputation

**Table 233: Clinical evidence summary: LMWH (standard dose) versus UFH**

| Outcomes | No of Participants | Quality of the evidence | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | (studies)<br>Follow up | (GRADE) | effect<br>(95% CI) | Risk with<br>UFH | Risk difference with LMWH (standard dose)<br>(95% CI) |
|---|---|---|---|---|---|
| DVT | 75<br>(1 study)<br>5-8 days post-op | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.83<br>(0.22 to 3.07) | 118 per 1000 | 20 fewer per 1000<br>(from 92 fewer to 244 more) |
| Major bleeding | 75<br>(1 study)<br>not reported | VERY LOW[a,b,d]<br>due to risk of bias, indirectness, imprecision | Not estimable[c] | Not estimable[c] | 0 fewer per 1000<br>(from 50 fewer to 50 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 Zero events in both arms. Risk difference calculated in Review Manager
d Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

## 39.4 Economic evidence

**Published literature**

No relevant health economic studies were identified.

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

## 39.5 Evidence statements

**Clinical**

*Strata: overall (no specific vascular population defined)*

Very low quality evidence from two studies (n=92) suggested a possible clinical benefit with unfractionated heparin (UFH) compared to no prophylaxis for a reduction in DVT in people undergoing vascular surgery, however this finding is seriously imprecise and could also be consistent with an increase in DVT rates. A possible clinical harm with UFH was suggested with an increase in major bleeding, although this too was an imprecise estimate that could also have been consistent with no difference. No difference was noted between UFH and no prophylaxis for PE. Very low quality evidence from one study (n=233) suggested that there were worse outcomes for all-cause mortality, DVT and thrombocytopaenia when using LMWH at a standard dose pre-operatively followed by a high-dose post-operatively compared to using UFH. However there was considerable uncertainty around these results with all of them also being consistent with possible benefit.

*Strata: People undergoing surgery for varicose veins*

High quality evidence from one study (n=1092) showed a clinically important reduction in DVT and PE when using either high-dose LMWH or unfractionated heparin (UFH) compared to no prophylaxis. Very low quality evidence from the same study suggested no difference between the LMWH and no prophylaxis for major bleeding rates, and a possible benefit of UFH over no prophylaxis, although these findings were imprecise. When comparing high-dose LMWH to no prophylaxis, there was low quality evidence for a possible reduction in DVT and very low quality evidence for a possible reduction in major bleeding when using LMWH. However there was uncertainty around these results. No difference was found between the two for PE rates.

Very low quality evidence from one study (n=262) showed no difference in DVT, PE or major bleeding rates when comparing either stockings or intermittent pneumatic compression and early mobilisation with the same mechanical and mobilisation strategy plus the addition of LMWH.

Very low quality evidence from one study (n=400) found no difference in rates of DVT, PE and major bleeding when using anti-embolism stockings compared to no prophylaxis. Moderate quality evidence from the same study suggested no difference with respect of patient reported outcomes on the Aberdeen Varicose Vein Symptoms Severity Score. Very low quality evidence also suggested no difference in patient-reported scores on the Venous Clinical Severity Score and the Chronic Venous Insufficiency Questionnaire, although these findings were imprecise.

*Strata: Lower limb amputation*

Very low quality evidence from one study (n=75) suggested there was no difference between LMWH (standard dose) and UFH for the outcomes of DVT and major bleeding in those undergoing lower limb amputation. These findings were imprecise.

**Economic**

No relevant economic evaluations were identified.

## 39.6 Recommendations and link to evidence

### 39.6.1 Open vascular surgery or endovascular aneurysm repair

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|---|---|
| **Recommendations** | **1.5.49 Consider pharmacological VTE prophylaxis with LMWH[kk] 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]**<br><br>**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:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression.**<br>**Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [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 (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.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Three studies were included in this section, which were of different populations including people undergoing vascular surgery including aortic or aortoiliac aneurysm repair, aorto-femoral bypass for atherosclerotic disease, and femoropopliteal or femorodistal bypass; people undergoing elective aortic bifurcation graft surgery; and people undergoing aortic reconstruction, carotid artery surgery, lumbar sympathectomy, leg revascularisation, psuedoaneurysm repair and repair of artiovenous fistulae.<br>All of the evidence was of very low quality for both UFH compared to no prophylaxis, and for LMWH compared to UFH. This was due to risk of bias, indirectness and imprecision. The outcomes for both studies were downgraded for indirectness as the |

[kk] 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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|---|---|
| | definition of the outcome of the study or the timepoint at which the outcome was measured did not match the protocol or was not reported. For DVT, both studies specified this was confirmed by fibrinogen scanning, which the committee did not consider to be an accurate measure of confirmation. |
| Trade-off between clinical benefits and harms | Many people having major arterial surgery are older and potentially immobile, putting them at risk for VTE. However many will already be receiving anticoagulation or antiplatelet therapy and therefore be at greater risk of bleeding or admitted with bleeding as emergencies. In addition, full dose heparin is frequently administered during surgery for arterial disease prior to arterial clamping. Major aortic procedures are done either by open techniques or more minimally invasive endovascular techniques but both tend to be long procedures often lasting several hours and both are associated with a significant risk of VTE. Post-operatively return to full mobility can be significantly delayed after vascular surgery especially for open procedures. The committee noted that there was little RCT evidence in the open vascular surgery population but given their likelihood of extended immobility they considered it would be appropriate for clinicians to consider pharmacological prophylaxis with LMWH for those at low risk of bleeding. For those people whose risk of bleeding outweighs their risk of VTE, the committee agreed mechanical prophylaxis could be considered. Given the lack of evidence identified for different forms of mechanical prophylaxis the committee considered it would best to offer clinicians the choice between AES and IPC. Most people who are vascular patients will have peripheral arterial disease; this means they are not usually able to use AES. Intermittent compression can be used but may impair postoperative mobilisation and rehabilitation.<br>Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee consider that mechanical prophylaxis offers little benefit once a patient is mobile. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials extrapolated from the abdominal surgery was between 7 and 10 days. |
| Trade-off between net clinical effects and costs | No economic studies were identified for this review. The unit costs were presented to the committee. The committee considered the clinical evidence presented for each stratum alongside the unit costs presented.<br><br>Based on the doses reported in the included clinical studies, the cost of using UFH (Heparin sodium) ranged from £9 to £59. Using the BNF recommended dose the cost was £24.6 (assuming administration for 7 days). For LMWH (enoxaparin sodium) the cost ranged from £24 to £91 (based on the included studies' doses). Using the BNF recommended dose the cost was £24.2 (assuming administration for 7 days). The cost of nurse time required for administration was higher for UFH compared to LMWH due to the higher frequency of administration. UFH also required more monitoring tests (full blood count).<br>Hence, LMWH was recommended as the preferred pharmacological prophylaxis modality as it was considered to be more cost effective, given the reduced frequency of administration and need for monitoring.<br>For those with contraindications to pharmacological prophylaxis, it was noted that AES are unlikely to be suitable due to the likelihood having peripheral arterial disease. In the absence of other suitable mechanical options the committee considered that IPC would be the only potential option and is likely to be cost effective in this population given their high VTE risk. |
| Other considerations | None. |

### 39.6.2 Lower limb amputation

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|---|---|
| **Recommendations** | **1.5.51 Consider pharmacological VTE prophylaxis with LMWH[ll] for a minimum of 7 days for people who are undergoing lower limb amputation whose risk of VTE outweighs their risk of bleeding. [2018]**<br><br>**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]**<br><br>**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]** |
| **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 (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.<br>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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | One study comparing LMWH to UFH was included. The quality of the data for DVT as an outcome was very low due to risk of bias and imprecision, and very low for major bleeding as this was additionally downgraded for indirectness as this was defined as any 'bleeding complications'. |
| Trade-off between clinical benefits and harms | There was a lack of direct evidence for the amputation population but those undergoing lower limb amputation are known to have a very high risk of VTE in the amputated leg due to surgical trauma and ligation of the vein, and they will be relatively immobile both before and after the surgery which also puts them at higher risk of VTE in the non-amputated leg. Most people who are vascular patients having amputation will have peripheral arterial disease; this means they are not usually able to use AES on the contralateral limb and not at all on the side of the amputation. Likewise, intermittent pneumatic compression can only be used on the contralateral limb. In view of their high risk and the unsuitability of mechanical methods, extrapolation from evidence in other high risk groups means it is likely that these patients will need pharmacological prophylaxis. If there is the occasional person who has a high bleeding risk such that pharmacological prophylaxis cannot be used, then due to their high risk of VTE they should receive mechanical prophylaxis on the contralateral leg.<br>Mechanical prophylaxis is recommended until the patient is back to normal mobility |

[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.

| | |
|---|---|
| | as the committee consider that mechanical prophylaxis offers little benefit once a patient is mobile. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials extrapolated from the abdominal surgery was between 7 and 10 days. |
| Trade-off between net clinical effects and costs | No economic studies were identified for this review. The unit costs were presented to the committee. The committee considered the clinical evidence presented for each stratum alongside the unit costs presented.<br>The clinical evidence showed that there was no clinical difference for LMWH compared to UFH with regard to DVT and major bleeding. Given the lower cost of LMWH compared to UFH it was considered to be the cost effective option, being equally effective and less costly. |
| Other considerations | None. |

### 39.6.3 Varicose vein surgery

| | |
|---|---|
| **Recommendations** | **1.5.54 Be aware that VTE prophylaxis is generally not needed for people undergoing varicose vein surgery where:**<br>• **total anaesthesia time is less than 90 minutes and**<br>• **the person is at low risk of VTE. [2018]**<br><br>**1.5.55 Consider pharmacological VTE prophylaxis with LMWH[mm], starting 6-12 hours after surgery and continuing for 7 days for people undergoing varicose vein surgery if:**<br>• **total anaesthesia time is more than 90 minutes or**<br>• **the person's risk of VTE outweighs their risk of bleeding. [2018]**<br><br>**1.5.56 Consider mechanical VTE prophylaxis with anti-embolism stockings, on admission, for people undergoing varicose vein surgery:**<br>• **who are at increased risk of VTE and**<br>• **when pharmacological prophylaxis is contraindicated. [2018]**<br><br>**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]** |
| **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 (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. |

[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.

| | |
|---|---|
| | 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 thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes.<br>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 that looked at prophylaxis in people undergoing varicose vein surgery.<br>One study (San Noberto 2013) focused on comparing mechanical prophylaxis (IPCD then AES) with and without LMWH. All of the evidence was of very low quality due to risk of bias and imprecision.<br>Another study (Wang 2015) compared both LMWH, UFH and no prophylaxis. Some evidence was of high quality; however the majority of evidence was of very low quality. The evidence for both LMWH versus no prophylaxis, and for UFH versus no prophylaxis with regards to DVT and PE, was of high quality, however the evidence for major bleeding was of low quality due to indirectness of the outcome definition. The evidence for LMWH compared to UFH with regards to DVT, PE and major bleeding was all of low quality due to imprecision. The committee noted that Wang 2015 used open vein surgery for varicose veins, which is not a type of surgery recommended by NICE for this condition.<br>Two further studies (Ayo 2017 and Ye 2016) compared anti-embolism stockings with no compression which were assessed as high risk of bias due to selection concerns and high rates of missing data. Some of the evidence was also downgraded due to intervention indirectness as patients were included in the study twice if they required bilateral treatment. Evidence was further downgraded due to imprecision around the effect estimates for the quality of life outcomes. |
| Trade-off between clinical benefits and harms | Varicose vein surgery is a relatively common procedure as varicose veins affect a large proportion of the population. The majority of people undergoing surgery for varicose veins are women; therefore oral contraceptive use and hormone replacement therapy use are common in this surgical population. Open varicose vein surgery is now becoming less common and more surgery is being performed using minimally invasive catheter techniques, often under local anaesthetic. People undergoing varicose vein surgery are considered to be at risk for VTE, and DVT and PE are the most common serious complications related to varicose vein surgery. The committee considered that the risk is high enough that pharmacological prophylaxis should be considered for at risk persons undergoing varicose vein surgery. Anti-embolism stockings were considered to be the preferred mechanical prophylaxis strategy in this population as they are usually mobile and not suitable for IPC.<br>Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a patient is mobile. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials extrapolated from the abdominal surgery was between 7 and 10 days. |
| Trade-off between net clinical effects and costs | No economic studies were identified for this review. The unit costs were presented to the committee. The committee considered the clinical evidence presented for each stratum alongside the unit costs presented.<br>The clinical evidence showed a possible benefit of LMWH for DVT and major bleeding but no difference for PE when compared with UFH. Given the lower cost of LMWH, it was considered to be the dominant pharmacological prophylaxis option in this population (more effective and less costly). |
| Other considerations | The committee noted that the rate of symptomatic DVT in varicose vein surgery is low, and that trials with a large number of participants are needed to reflect the true |

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| | rate of DVT. This committee noted that the low number of participants in the included studies meant that the studies did not accurately represent the rate of DVT in this population. |

# 40 Head and neck surgery

## 40.1 Oral and maxillofacial surgery

### 40.1.1 Introduction

Oral and maxillofacial operations are common procedures that are usually undertaken as day cases. Individuals undergoing these procedures are generally mobile. The risk of VTE in this population is therefore generally low. However, individual factors could increase this risk and need to be considered when making a decision about the provision and choice of prophylaxis. Additionally, some cases undergo longer procedures and may have associated risk factors such as cancer. In the last version of this guideline (CG92), this population was covered under "other surgeries"; however, a separate review was necessary so that a specific recommendation for this population could be made.

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

For full details see review protocol in appendix C.

**Table 234: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults and young people (16 years and older) undergoing oral or maxillofacial surgery who are:<br>• Admitted to hospital<br>• Having day procedures<br>• Outpatients post-discharge |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>  ○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*)<br>  ○ 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*)<br>  ○ 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*)<br>• LMWH, licensed in countries other than UK:<br>  ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>  ○ Certoparin (3000 units daily)<br>  ○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to |

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| | maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300 mg)*<br><br>*off-label |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br><br>Important outcomes:<br>• 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) |

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| | • Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Cerebral sinus thrombosis (30 days) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

### 40.1.3 Clinical evidence

No relevant clinical studies comparing difference pharmacological and mechanical prophylaxis strategies for people who are undergoing oral or maxillofacial surgery. See the study selection flow chart in appendix E and excluded studies list in appendix N.

### 40.1.4 Economic evidence

#### Published literature

No relevant health economic studies were identified.

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

### 40.1.5 Evidence statements

#### Clinical

No relevant clinical studies were identified.

#### Economic

No relevant economic evaluations were identified.

### 40.1.6 Recommendations and link to evidence

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|---|---|
| **Recommendations** | **1.5.58 Consider pharmacological VTE prophylaxis with LMWH[nn] for a minimum of 7 days for people undergoing oral or maxillofacial surgery whose risk of VTE outweighs their risk of bleeding. [2018]**<br><br>**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:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression.**<br><br>**Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [2018]** |
| **Research recommendation** | **None** |
| Relative values of | The committee considered all-cause mortality (up to 90 days from hospital |

[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.

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| different outcomes | 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.<br>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 thrombocytopaenia (duration of study), technical complications of mechanical interventions (duration of study) and cerebral sinus thrombosis as important outcomes.<br>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.<br>In the absence of evidence, the committee agreed to consider the evidence for specific prophylaxis choices from other surgery populations as indirect evidence to inform the recommendations for people undergoing oral or maxillofacial surgery, with particular reference to the abdominal surgery population. |
| Trade-off between clinical benefits and harms | No relevant clinical studies were identified. The committee noted that a person's risk of VTE needs to be considered when deciding if VTE prophylaxis is appropriate. VTE prophylaxis reduces the risk of VTE but pharmacological methods of prophylaxis can increase the risk of bleeding and mechanical methods prophylaxis can have technical complications, which need to be weighed against the reduction in VTE risk. The committee noted that the decision about whether pharmacological or mechanical prophylaxis is appropriate should be based on clinical judgement taking into account bleeding risk and individual circumstances. The committee agreed that pharmacological prophylaxis should be considered for those with a high risk of VTE and a low risk of bleeding, and that mechanical prophylaxis should be considered for those with a high risk of VTE and a high risk of bleeding, such as for people undergoing oral/maxillofacial surgery for cancer.<br>Many people undergoing oral or maxillofacial surgery are day cases, or if not, are usually mobile fairly quickly following surgery (for example people having surgery for wisdom teeth or other dentoalvaolar surgery procedures). Therefore these people are often low risk and may not require prophylaxis. However for some patients, such as those having major head and neck surgery or orthognathic surgery who are immobile after surgery; those with active cancer; or those assessed as at high risk for cerebral sinus thrombosis, prophylaxis may be necessary.<br>Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a patient is mobile. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials extrapolated from the abdominal surgery was between 7 and 10 days.<br>In the absence of evidence the committee considered it would be appropriate to make a softer 'consider' recommendation. |
| Trade-off between net clinical effects and costs | No relevant economic studies were identified. Unit costs were presented. In the absence of both clinical and economic evidence, the committee determined that the decision to prescribe prophylaxis should be made on an individual basis, taking into account the individual's risk of VTE and the benefit-harm balance of the proposed prophylaxis strategies. For those at high risk of VTE, the committee considered that prophylaxis is likely to be cost effective. The choice of the prophylaxis method will depend on the individual's risk of bleeding and the presence of contraindications. |
| Other considerations | The committee noted that in current practice people undergoing oral or maxillofacial surgery generally do not have pharmacological prophylaxis as much of the minor surgery is performed under local anaesthesia in a fully ambulatory patient. In surgery requiring general anaesthesia, pharmacological prophylaxis is not used but all have |

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| | mechanical prophylaxis with AES. In the more major maxillofacial procedures the full VTE prophylaxis algorithm is considered appropriate.<br>The committee also noted that this guideline only covers patients who are admitted for care. Admission in the context of this guideline refers to admission as an inpatient, where a bed is provided for one or more nights or admission as a day patient, where a bed will be provided for a procedure including surgery or chemotherapy but not for an overnight stay. If dental patients are not considered as admitted then they do not fall within the remit of this guideline. |

# 40.2 ENT surgery

## 40.2.1 Introduction

Ear, nose and throat (ENT) procedures are fairly common, however the majority of ENT procedures are usually undertaken as day cases. With the exception of major surgery such as those undertaken for cancer, people undergoing these procedures are likely to be mobile. Current practice in terms of risk assessment and prophylaxis provision for this population is variable. This population was covered in the last version of this guideline (CG92) under "other surgeries"; however, a separate review was necessary so that a specific recommendation for this population could be made.

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

For full details see review protocol in appendix C.

**Table 235: PICO characteristics of review question**

| | |
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| **Population** | Adults and young people (16 years and older) undergoing ear, nose or throat (ENT) who are:<br>• Admitted to hospital<br>• Having day procedures<br>• Outpatients post-discharge |
| **Intervention(s)** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br>• Vena caval filters<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously)<br>• Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60 mg twice daily*)<br>○ 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*)<br>○ tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 |

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| | twice daily*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300 mg)*<br><br>*off-label |
| **Comparison(s)** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days from hospital discharge)<br>• 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)<br>• 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<br>• 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<br>• 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<br><br>Important outcomes: |

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| | • 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.<br>• Health-related quality of life (validated scores only)(up to 90 days from hospital discharge)<br>• Heparin-induced thrombocytopaenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Cerebral sinus thrombosis (up to 30 days from hospital discharge) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

### 40.2.3 Clinical evidence

No relevant clinical studies comparing different pharmacological and mechanical prophylaxis strategies for people who are undergoing ears, nose and throat (ENT) surgery were identified. See the study selection flow chart in appendix E and excluded studies list in appendix N.

### 40.2.4 Economic evidence

#### Published literature

No relevant health economic studies were identified.

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

### 40.2.5 Evidence statements

#### Clinical

No relevant clinical studies were identified.

#### Economic

No relevant economic evaluations were identified.

### 40.2.6 Recommendations and link to evidence

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| **Recommendations** | **1.5.60 Consider pharmacological VTE prophylaxis with LMWH[oo] 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]**<br><br>**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:**<br>• **anti-embolism stockings or**<br>• **intermittent pneumatic compression.**<br><br>**Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [2018]** |

[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.

| Research recommendation | None |
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| 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.<br><br>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 thrombocytopaenia (duration of study), technical complications of mechanical interventions (duration of study) and cerebral sinus thrombosis as important outcomes.<br><br>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 studies were identified.<br><br>In the absence of evidence, the committee agreed to consider the evidence for specific prophylaxis choices from other surgery populations as indirect evidence to inform the recommendations for people undergoing ENT surgery, with particular reference to the abdominal surgery population. However it was acknowledged that ENT surgery is different from abdominal surgery as it does not involve a body cavity. |
| Trade-off between clinical benefits and harms | No relevant clinical studies were identified. The committee noted that a person's risk of VTE needs to be considered when deciding if VTE prophylaxis is appropriate. VTE prophylaxis reduces the risk of VTE but pharmacological methods of prophylaxis can increase the risk of bleeding and mechanical methods prophylaxis can have technical complications, which need to be weighed against the reduction in VTE risk. The committee noted that the decision about whether pharmacological or mechanical prophylaxis is appropriate should be based on clinical judgement taking into account bleeding risk and individual circumstances. The committee agreed that pharmacological prophylaxis should be considered for those with a high risk of VTE and a low risk of bleeding, and that mechanical prophylaxis should be considered for those with a high risk of VTE and a high risk of bleeding, such as for people undergoing ENT surgery for cancer.<br><br>Overall, the committee considered that most people undergoing ENT procedures are fully mobile day cases and therefore are often low risk for VTE and may not require prophylaxis. However, in high risk people, such as those with active cancer or those who are immobile after surgery, prophylaxis may be necessary.<br><br>Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a patient is mobile. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials extrapolated from the abdominal surgery was between 7 and 10 days.<br><br>In the absence of evidence the committee considered it would be appropriate to make a softer 'consider' recommendation. |
| Trade-off between net clinical effects and costs | No relevant economic studies were identified. Unit costs were presented. In the absence of both clinical and economic evidence, the committee determined that the decision to prescribe prophylaxis should be made on an individual basis, taking into account the individual's risk of VTE and the benefit-harm balance of the proposed prophylaxis strategies. For those at high risk of VTE, the committee considered that prophylaxis is likely to be cost effective. The choice of the prophylaxis method will depend on the individual's risk of bleeding and the presence of contraindications. |
| Other considerations | The committee noted that in current practice the majority of people undergoing ENT |

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| | surgery do not have pharmacological prophylaxis but all have mechanical prophylaxis with AES. |

# 41 Acronyms and abbreviations

| Acronym or abbreviation | Description |
|---|---|
| ACS | Acute coronary syndromes |
| AES | Anti-embolism stockings |
| BNF | British National Formulary |
| CEA | Cost-effectiveness analysis |
| CI | Confidence interval |
| CPM | Continuous passive motion |
| CRT | Catheter related thrombosis |
| CUA | Cost-utility analysis |
| CVC | Central venous catheters |
| DOAC | Direct oral anticoagulant |
| DVT | Deep vein thrombosis |
| FID | Foot impulse devices |
| GCS | Graduated compression stockings |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HAT | Hospital acquired thrombosis or hospital associated thrombosis |
| HD | High dose |
| HES | Hospital Episode Statistics |
| HIT | Heparin-induced thrombocytopaenia |
| ICER | Incremental cost-effectiveness ratio |
| ICU | Intensive Care Unit |
| IPCD | Intermittent pneumatic compression devices |
| ISS | Injury severity score |
| IV | Intravenous |
| LD | Low dose |
| LMWH | Low molecular weight heparin |
| LOS | Length of stay |
| MB | Major bleeding |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| NMA | Network meta-analysis |
| NMES | Neuromuscular electrical stimulation |
| NNT | Number needed to treat |
| OAC | Oral anticoagulants |
| PASA | NHS Purchasing and Supply Agency |
| PE | Pulmonary embolism |
| PHT | Chronic thromboembolic pulmonary hypertension |
| PTS | Post-thrombotic syndrome |
| SC | Subcutaneous |
| TESS | Trauma Embolic Scoring System |
| UKOSS | United Kingdom Obstetric Surveillance System |
| UFH | Unfractionated heparin |
| VKA | Vitamin K antagonist |

| Acronym or abbreviation | Description |
|---|---|
| VTE | Venous thromboembolism |

# 42 Glossary

The NICE Glossary can be found at www.nice.org.uk/glossary.

## 42.1 Guideline-specific terms

| Term | Definition |
|---|---|
| Acute medical admissions | A medical admission concerned with the immediate and early specialist management of adult patients suffering from a wide range of medical conditions who present to, or from within, hospitals, requiring urgent or emergency care. |
| Adherence | The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor's recommendation. |
| Admission | Admission in the context of this guideline refers to admission as an inpatient, where a bed is provided for one or more nights or admission as a day patient, where a bed will be provided for a procedure including surgery or chemotherapy but not for an overnight stay. |
| Anticoagulants | Any agent used to prevent the formation of blood clots. These include oral agents, such as warfarin, and others which are injected into a vein or under the skin, such as heparin. |
| Anti-embolism stockings | Hosiery which, when worn on the leg, exerts graduated compression on the leg surface and is intended to reduce the incidence of deep vein thrombosis. These should not be confused with "graduated compression stockings" which have a different pressure profile and are not used for the prevention of venous thromboembolism. |
| Chronic thromboembolic pulmonary hypertension | Abnormally elevated blood pressure within the pulmonary circuit (pulmonary artery). |
| Comorbidity | Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual. |
| Continuous passive motion | Where a joint is moved continuously, either by another person bending it or by a machine. |
| Deep vein thrombosis (DVT) | Venous thrombosis that occurs in the "deep veins" in the legs, thighs, or pelvis. |
| Discharge | Discharge in the context of this guideline refers to discharge from hospital as an inpatient or after a day procedure. |
| Distal | Refers to a part of the body that is farther away from the centre of the body than another part. |
| Dosage | The prescribed amount of a drug to be taken, including the size and timing of the doses. |
| DVT | See 'Deep-vein thrombosis'. |
| Elective | Name for clinical procedures that are regarded as advantageous to the patient but not urgent. |
| Electrical stimulation | Electrical stimulation or neuromuscular electrical stimulation is designed to increase venous blood flow velocity out of the leg to reduce the incidence of post-surgical venous thrombosis. |
| Emergency admission | When admission is unpredictable and at short notice because of clinical need. |
| Fetal/fetus | A human being or animal in its later stages of development before it is born. |
| Foot impulse devices (FID) | see Intermittent pneumatic compression. |

| Term | Definition |
|---|---|
| Heparin-induced thrombocytopaenia (HIT) | Low blood platelet count resulting from the administration of heparin (or heparin-like agents). Despite having a low platelet count, patients with this condition are at high risk of their blood clotting. |
| HIT | See 'Heparin-induced thrombocytopaenia'. |
| Hospital-acquired thrombosis (HAT) or Hospital acquired venous thromboembolism | Hospital-acquired or hospital-associated thrombosis (HAT), also known as hospital acquired venous thromboembolism or hospital associated thrombosis, covers all venous thromboembolism (VTE) that occurs in hospital and within 90 days after hospital admission. |
| Indication | The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA). |
| Intermittent pneumatic compression | A method of prophylaxis that includes an air pump and inflatable garments in a system designed to improve venous circulation in the lower limbs of people at risk of deep vein thrombosis or pulmonary embolism.<br>The inflation-deflation cycle of IPC therapy simulates the thigh, calf and foot's normal ambulatory pump action increasing both the volume and rate of blood flow, eliminating venous stasis and replicating the effects of the natural muscle pump.<br>Intermittent pneumatic compression devices can be thigh or knee length sleeves that are wrapped around the leg, or a garment that can be wrapped around or worn on the foot that is designed to mimic the actions of walking (foot-pump). |
| Intermittent pneumatic compression devices (IPCD) | see Intermittent pneumatic compression. |
| Intervention | Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy. |
| Intraoperative | The period of time during a surgical procedure. |
| Length of stay (LOS) | The total number of days a patient stays in hospital. |
| Licence | See 'Product licence'. |
| Lower limb immobilisation | Defined as any clinical decision taken to manage the affected limb in such a way as to prevent normal weight bearing status and/or use of that limb. |
| Mechanical | Physical (as opposed to chemical) agent used, in this context, to reduce likelihood of thrombosis. Mechanical methods of DVT prophylaxis work to combat venous stasis and include: anti-embolism stockings, intermittent pneumatic compression devices (IPCD), foot impulse devices, also known as foot pumps (FID). |
| Medical devices | All products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or handicap. |
| Medicines and Healthcare Products Regulatory Agency (MHRA) | The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely. |
| Neuromuscular electrical stimulation | See 'Electrical stimulation' |
| Off-label | A drug or device used treat a condition or disease for which it is not specifically licensed. |
| Older people | People over the age of 65 years. |
| PE | See 'Pulmonary embolism'. |
| Perioperative | The period from admission through surgery until discharge, encompassing pre-operative and post-operative periods. |
| Post-thrombotic (Post- | Chronic pain, swelling, and occasional ulceration of the skin of the leg that |

| Term | Definition |
|---|---|
| phlebitic) Syndrome | occur as a consequence of previous venous thrombosis. |
| Postoperative | Pertaining to the period after patients leave the operating theatre, following surgery. |
| Preoperative | Pertaining to the period before surgery commences. |
| Primary care | Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians. |
| Product licence | An authorisation from the MHRA to market a medicinal product. |
| Prognosis | A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes. |
| Prophylaxis | A measure taken for the prevention of a disease. |
| Proximal | Refers to a part of the body that is closer to the centre of the body than another part. |
| Pulmonary embolism (PE) | A blood clot that breaks off from the deep veins and travels round the circulation to block the pulmonary arteries (arteries in the lung). Most deaths arising from DVT are caused by PE. |
| Pulmonary hypertension | See 'Chronic thromboembolic pulmonary hypertension'. |
| Renal impairment | People with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m$^2$. More information about renal disease is available from https://www.nice.org.uk/guidance/cg182/chapter/Introduction. |
| Significantly reduced mobility | Defined by the committee as:<br>'patients who are bed bound, unable to walk unaided or likely to spend a substantial proportion of their day in bed or in a chair' |
| Thrombophilia | The genetic or acquired prothrombotic states that increase the tendency to venous thromboembolism. It is a condition which leads to a tendency for a person's blood to clot inappropriately. |
| Thromboprophylaxis | A measure taken to reduce the risk of thrombosis. |
| Treatment options | The choices of intervention available. |
| Venous thromboembolism (VTE) | The blocking of a blood vessel by a blood clot dislodged from its site of origin. It includes both DVT and PE. |
| Venous thrombosis (VT) | A condition in which a blood clot (thrombus) forms in a vein. |

## 42.2 General terms

| Term | Definition |
|---|---|
| Abstract | Summary of a study, which may be published alone or as an introduction to a full scientific paper. |
| Allocation concealment | The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants. |
| Applicability | How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered. |
| Arm (of a clinical study) | Subsection of individuals within a study who receive one particular intervention, for example placebo arm. |
| Association | Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal. |

| Term | Definition |
|---|---|
| Base case analysis | In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis. |
| Baseline | The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared. |
| Bayesian analysis | A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior'). |
| Before-and-after study | A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs. |
| Bias | Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias. |
| Blinding | A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.<br>A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received. |
| Carer (caregiver) | Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability. |
| Clinical efficacy | The extent to which an intervention is active when studied under controlled research conditions. |
| Clinical effectiveness | How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials.<br>Clinical effectiveness is not the same as efficacy. |
| Clinician | A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist. |
| Cochrane Review | The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). |
| Cohort study | A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study. |
| Comorbidity | A disease or condition that someone has in addition to the health problem being studied or treated. |
| Comparability | Similarity of the groups in characteristics likely to affect the study results |

| Term | Definition |
|---|---|
| | (such as health status or age). |
| Confidence interval (CI) | There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population.<br>The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110". In such a case the 95% CI would be 110 to 150.<br>A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied). |
| Confounding factor | Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with.<br>For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor. |
| Consensus methods | Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques. |
| Control group | A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences.<br>Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment. |
| Cost–benefit analysis (CBA) | Cost–benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs. |
| Cost–consequences analysis (CCA) | Cost–consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost–benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out. |
| Cost-effectiveness analysis (CEA) | Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention). |
| Cost-effectiveness model | An explicit mathematical framework, which is used to represent clinical |

| Term | Definition |
|---|---|
| | decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes. |
| Cost–utility analysis (CUA) | Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility. |
| Credible interval (CrI) | The Bayesian equivalent of a confidence interval. |
| Decision analysis | An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes. |
| Deterministic analysis | In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis |
| Discounting | Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present. |
| Disutility | The loss of quality of life associated with having a disease or condition. See Utility |
| Dominance | A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative. |
| Drop-out | A participant who withdraws from a trial before the end. |
| Economic evaluation | An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals.<br>There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost-minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention. |
| Effect<br>(as in effect measure, treatment effect, estimate of effect, effect size) | A measure that shows the magnitude of the outcome in one group compared with that in a control group.<br>For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%.<br>The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant). |
| Effectiveness | How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care. |
| Efficacy | How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care. |
| EQ-5D (EuroQol 5 dimensions) | A standardised instrument used to measure health-related quality of life. It provides a single index value for health status. |
| Evidence | Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients). |

| Term | Definition |
|---|---|
| Exclusion criteria (literature review) | Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence. |
| Exclusion criteria (clinical study) | Criteria that define who is not eligible to participate in a clinical study. |
| Extended dominance | If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore cost effective and should be preferred, other things remaining equal. |
| Extrapolation | An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics. |
| Follow-up | Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables. |
| Generalisability | The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity. |
| GRADE, GRADE profile | A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile. |
| Harms | Adverse effects of an intervention. |
| Health economics | Study or analysis of the cost of using and distributing healthcare resources. |
| Health-related quality of life (HRQoL) | A measure of the effects of an illness to see how it affects someone's day-to-day life. |
| Heterogeneity<br>or Lack of homogeneity | The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity. |
| Imprecision | Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect. |
| Inclusion criteria (literature review) | Explicit criteria used to decide which studies should be considered as potential sources of evidence. |
| Incremental analysis | The analysis of additional costs and additional clinical outcomes with different interventions. |
| Incremental cost | The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently. |
| Incremental cost-effectiveness ratio (ICER) | The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another. |
| Incremental net benefit (INB) | The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 × QALYs gained) − Incremental cost. |
| Indirectness | The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome). |

| Term | Definition |
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| Intention-to-treat analysis (ITT) | An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it. |
| Intervention | In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet. |
| Intraoperative | The period of time during a surgical procedure. |
| Length of stay | The total number of days a participant stays in hospital. |
| Licence | See 'Product licence'. |
| Life years gained | Mean average years of life gained per person as a result of the intervention compared with an alternative intervention. |
| Logistic regression or Logit model | In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit'). |
| Loss to follow-up | A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial |
| Markov model | A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle). |
| Meta-analysis | A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment. |
| Multivariate model | A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable. |
| Negative predictive value (NPV) | In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: TN/(TN+FN) |
| Net monetary benefit (NMB) | The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NMB for an intervention is calculated as: (£20,000 × mean QALYs) − mean cost.<br>The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB. |
| Non-randomised intervention study | A quantitative study investigating the effectiveness of an intervention that does not use randomisation to allocate patients (or units) to treatment groups. Non-randomised studies include observational studies, where allocation to groups occurs through usual treatment decisions or people's preferences. Non-randomised studies can also be experimental, where the investigator has some degree of control over the allocation of treatments.<br>Non-randomised intervention studies can use a number of different study designs, and include cohort studies, case–control studies, controlled before-and-after studies, interrupted-time-series studies and quasi-randomised controlled trials. |

| Term | Definition |
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| Observational study | Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening.<br>There is a greater risk of selection bias than in experimental studies. |
| Odds ratio | Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another.<br>An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group.<br>Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio. |
| Opportunity cost | The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention. |
| Outcome | The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins. |
| P value | The p value is a statistical measure that indicates whether or not an effect is statistically significant.<br>For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant.<br>If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be. |
| Perioperative | The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods. |
| Placebo | A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what |

| Term | Definition |
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| | effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention. |
| Polypharmacy | The use or prescription of multiple medications. |
| Posterior distribution | In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood). |
| Positive predictive value (PPV) | In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: TP/(TP+FP) |
| Postoperative | Pertaining to the period after patients leave the operating theatre, following surgery. |
| Power (statistical) | The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed. |
| Preoperative | The period before surgery commences. |
| Prior distribution | In Bayesian statistics this is the probability distribution for a statistic based on previous evidence or belief. |
| Primary care | Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians. |
| Primary outcome | The outcome of greatest importance, usually the one in a study that the power calculation is based on. |
| Probabilistic analysis | In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis. |
| Product licence | An authorisation from the MHRA to market a medicinal product. |
| Prognosis | A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes. |
| Prospective study | A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies. |
| Publication bias | Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot. |
| Quality of life | See 'Health-related quality of life'. |
| Quality-adjusted life year (QALY) | A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.<br>QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance. |
| Randomisation | Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For |

| Term | Definition |
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| | example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention. |
| Randomised controlled trial (RCT) | A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias. |
| RCT | See 'Randomised controlled trial'. |
| Receiver operated characteristic (ROC) curve | A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal. |
| Reporting bias | See 'Publication bias'. |
| Resource implication | The likely impact in terms of finance, workforce or other NHS resources. |
| Retrospective study | A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected. |
| Review question | In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations. |
| Risk ratio (RR) | The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke).<br>If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk. |
| Secondary outcome | An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes. |
| Selection bias | Selection bias occurs if:<br>a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or<br>b) There are differences between groups of participants in a study in terms of how likely they are to get better. |
| Sensitivity | How well a test detects the thing it is testing for.<br>If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive').<br>For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant.<br>If the same test were more specific (sometimes referred to as having |

| Term | Definition |
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| | higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative').<br>Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed. |
| Sensitivity analysis | A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.<br>One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.<br>Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated.<br>Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.<br>Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation). |
| Significance (statistical) | A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$). |
| Specificity | The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases.<br>See related term 'Sensitivity'.<br>In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers. |
| Stakeholder | An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be:<br>• manufacturers of drugs or equipment<br>• national patient and carer organisations<br>• NHS organisations<br>• organisations representing healthcare professionals. |
| State transition model | See Markov model |
| Systematic review | A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis. |
| Time horizon | The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation. |
| Transition probability | In a state transition model (Markov model), this is the probability of moving from one health state to another over a specific period of time. |
| Treatment allocation | Assigning a participant to a particular arm of a trial. |

| Term | Definition |
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| Univariate | Analysis which separately explores each variable in a data set. |
| Utility | In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs). |

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