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

Population	Adults and young people (16 years and older) with lower limb immobilisation who are: • Admitted to hospital • Having day procedures • Outpatients post-discharge Immobilisation is defined as any clinical decision taken to manage the affected limb in such a way as to prevent normal weight bearing status and/or use of that limb.
Intervention(s)	Mechanical: • Anti-embolism stockings (AES) (above or below knee) • Intermittent pneumatic compression (IPCD) devices (full leg or below knee) • Foot pumps or foot impulse devices (FID) • Electrical stimulation (including Geko devices) Pharmacological: • Unfractionated heparin (UFH) (low dose, administered subcutaneously) • Low molecular weight heparin (LMWH), licensed in UK: ○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) ○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) ○ tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) • LMWH, licensed in countries other than UK: ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) ○ Certoparin (3000 units daily) ○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) ○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to

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

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

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 Intervention (n=157): Fondaparinux 2.5mg. For the duration of immobilisation, mean (SD) 38.0 (8.7) days Comparison (n=156): no VTE prophylaxis. For the duration of immobilisation, mean (SD) 40.3 (8.6) days	n=467 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. Adults (mean age LMWH 47.7, fondaparinux 49.7, control 44.5) Male to female ratio 118:160 The Netherlands	DVT (40 days): verified by duplex sonography PE (40 days): verified by CT angiography 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 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) Male to female ratio 1:1 Sweden		
Domeij-arverud 2015[77]	Intervention (n=74): IPCD, calf. Fitted bilaterally, beneath plaster cast on operated leg. Duration 2 weeks post-op Comparison (n=74): no VTE prophylaxis	n=148 People with plaster cast due to acute unilateral tendo Achilles rupture Adults (mean 40.9 years; range 26-62) Male to female ratio 88:21 Sweden	PE (42 days): CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography 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. Comparison (n=152): no VTE prophylaxis	n=300 People with below knee plaster casts on lower extremity. Reasons for plaster cast: fracture 73.3%, tendon rupture 20.3%, other 6.3% Adults (>18 years; mean 49 years) Male to female ratio 128:172 Denmark	PE (mean 38 days): method of confirmation not reported 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]) Comparison (n=163	n=428 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% 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 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 Germany		
Kujath 1993 [172]	Intervention (n=126): 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) Comparison (n=127): no VTE prophylaxis. Mean period of plaster cast 15.8 [9.6] days, range 5-66)	n=306 People with plaster cast. Reason for plaster cast: soft tissue injury 70%, fractures 30% Young people (aged >16 years; mean intervention 32.9±13.8, comparison 35.6±14.6 Male to female ratio 146:107 Germany	DVT (until plaster cast removed): diagnosed by ultrasound confirmed by venography	Included in CG92
Lapidus 2007A [178]	Intervention (n=52): LMWH, standard dose (Dalteparin 5000U). Started within hours post-surgery, up to 6th week, or mobilisation Comparison (n=53): No VTE prophylaxis (placebo)	n=105 People with below knee plaster cast due to Achilles tendon rupture Adults (mean 40 years, range 18-75) Male to female ratio 83:22 Sweden	All-cause mortality (42 days) PE, fatal (42 days): method of confirmation not reported PE (42 days) : method of confirmation not reported 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 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 Comparison (n=136): No VTE prophylaxis (placebo)	People with lower limb immobilisation (82% plaster cast, 18% orthosis), due to acute ankle fracture Adults (mean years 48, range 18-76) Male to female ratio 124:148 Sweden	PE, fatal (42 days): method of confirmation not reported PE (42 days): confirmed by: ventilation perfusion scan or spiral CT if suspected 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 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. Comparison (n=223): no VTE prophylaxis. Mean duration of immobilisation: 44 days.	n=440 People with plaster cast (84.3%) or brace, due to fracture of leg (80%) or rupture of Achilles tendon (20%) Adults (median 47 years; range 37-55) Male to female ratio 112:105 Denmark	DVT (until plaster cast removed): diagnosed by unilateral venography within a week of plaster cast removal PE (until plaster cast removed): confirmed by ventilation perfusion scanning 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 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 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) 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. 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. 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% Adults (≥18 years; mean 46) Male to female ratio 1:1 Multicentre international	DVT (21-45 days): confirmed by ultrasongraphy 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 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 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. Comparison (n=131): no VTE prophylaxis. Mean immobilisation duration 42 (29) days. Concurrent medication: Aspirin and other	n=265 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 Adults (mean 48 years; range 18-87 Male to female ratio 139:126 Canada	PE (90 days): confirmed by positive spiral computed tomography pulmonary angiogram, high probability V/Q lung scan, or leg imaging DVT (90 days): confirmed by bilateral Doppler ultrasound 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 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. Comparison (n=131): no VTE prophylaxis. Mean immobilisation duration 4.9 (2.5) weeks. Concurrent medication: none reported	n = 1435 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% Adults mean age (SD): LMWH 46.5 (16.5); no prophylaxis 45.6 (16.4) years Male to female ratio 716/719 The Netherlands	PE (3 months): not defined Symptomatic DVT (3 months): not defined Major bleeding (3 months): not defined 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.

	to 45 days from hospital discharge) as critical outcomes. The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), heparin-induced thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	The 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. 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. 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. 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. 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. 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. 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

	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. 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. 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. 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.