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: • Admitted to hospital • Outpatients post-discharge
Intervention(s)	Mechanical: • Anti-embolism stockings (AES) (above or below knee) • Intermittent pneumatic compression (IPCD) devices (full leg or below knee) • Foot pumps or foot impulse devices (FID) • Electrical stimulation (including Geko devices) • Continuous passive motion 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) • 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): LMWH, enoxaparin, 40mg once daily (standard dose) subcutaneously given along with placebo (saline). From 12±2 hours preoperatively and continued for 5-9 days. Comparison (n=849): Fondaparinux, 2.5mg, once daily, subcutaneously given along with placebo (saline). From 6±2 hours postoperatively and continued for 5-9 days.	n=1711 People undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck Age (mean): 79 years Gender (male to female ratio): 1:3 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) DVT (symptomatic and asymptomatic) (11 days): confirmed by systemic ascending bilateral contrast venography 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: AES was permitted, 49% of patients used AES. Early mobilisation was strongly recommended.	Netherlands, UK	Fatal PE (11 days): confirmed at autopsy 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): 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. Comparison (n=329): 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. Concomitant treatment: AES was permitted, 46% of patients used AES. Early mobilisation was strongly recommended.	n=656 People undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck Age (median): 79 years Gender (male to female ratio): 1:2 Argentina, Australia, Belgium, Czech Republic, Denmark, Finland, France, Greece, Italy, Poland, Portugal, Spain, Sweden, Switzerland, the Netherlands, UK	All-cause mortality (25-32 days) DVT (symptomatic and asymptomatic) (25-32 days): confirmed by systemic ascending bilateral contrast venography PE (25-31 days): confirmed by high-probability lung scanning, pulmonary angiography, spiral computed tomography Fatal PE (25-31 days): confirmed at autopsy 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. Comparison (n=100): Control group, no prophylaxis, no further details reported.	n=200 People admitted with sub-capital or pertrochanteric fracture of the femur Age (mean): 76 years Gender (male to female ratio): 1:5 Norway	All-cause mortality (90 days) DVT (symptomatic and asymptomatic) (90 days): definition not reported PE (90 days): definition not reported 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. Comparison (n=159): Control group, received same clinical care as the intervention group. Concomitant treatment: Physiotherapy, active mobilisation regimen which started on postoperative day 1	n=304 People admitted with pelvic, acetabular, femoral neck, intertrochanteric, or sub-trochanteric fractures Age: 80% >40 years Gender (male to female ratio): Not reported Canada	DVT (symptomatic and asymptomatic) (mean: 14 days): confirmed by Doppler ultrasonography 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 People who admitted for intertrochanteric or trans-cervical femoral fractures Age (mean): not reported Gender: 100% female UK	All-cause mortality (time-point not reported) DVT (symptomatic and asymptomatic) (time-point not reported): confirmed by venography	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	reported) Comparison (n=50): Control group, no prophylaxis (usual care)		PE (time-point not reported): confirmed by clinical and radiological examinations or at autopsy Wound infection/haematoma (time-point not reported)	
Goel 2009 [114]	Intervention (n=157) 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. Comparison (n=148) No prophylaxis, saline given subcutaneously once daily for 14 days	n=305 People admitted with unilateral isolated fractures below the knee which require operative fixation Age (mean): 40.95 years Gender (male to female ratio): 1.6:1 Canada	All-cause mortality (time-point not reported) DVT (symptomatic and asymptomatic) (14 days): confirmed by bilateral venography 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): Vitamin K antagonist, phenindione, prothrombin time to 2-2.5 times the control (prothrombin time not reported). Duration of intervention not clearly reported. Comparison (n=38): Control group, no further details	n=76 People admitted for a hip fracture Age (mean): 77 years Gender (male to female ratio): 1:5 Canada	All-cause mortality (time-point not reported) DVT (symptomatic and asymptomatic) (5-12 days): confirmed by ascending phlebography Major bleeding (time-point not	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	reported.		reported): patients requiring blood transfusions Deep wound infection (time-point not reported)	
Jørgensen 1992[154]	Intervention (n=30): 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. Comparison (n=38): Placebo, isotonic sodium chloride, from 2 hours preoperatively. Second injection administered 12 hours postoperatively. Placebo administered once daily thereafter for 6 days.	n=68 People admitted for a hip fracture Age (mean): 80 years Gender (male to female ratio): 1:3 Denmark	All-cause mortality (84 days) DVT (symptomatic and asymptomatic) (9 days): confirmed by I^{125} fibrinogen uptake test and scans and ascending phlebography PE (84 days): definition not reported Superficial wound infection (84 days)	Included in CG92
Lahnborg 1980 [174]	Intervention (n=71): Unfractionated heparin, sodium heparin, 5000IU subcutaneously, every 12 hours for 10 days, started 2-3 hours after the operation. Comparison (n=69): Placebo, 0.5ml of 0.85% saline, subcutaneously every 12 hours for 10 days, started 2-3 hours after the operation	n=140 People admitted for nailing of a fractured neck of the femur Age (mean): 77 years Gender (male to female ratio): 1:2 Sweden	DVT (symptomatic and asymptomatic) (10 days): confirmed by I^{125} fibrinogen uptake test and scans PE (time-point not reported): 'diagnosed clinically'	Included in CG92
Monreal 1989[218]	Intervention (n=46): LMWH, dalteparin, 5000IU once daily (standard dose), subcutaneously given	n=90 People admitted for a hip fracture	All-cause mortality (time-point not reported) 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. Comparison (n=44): Unfractionated heparin, 5000IU, subcutaneously given every 8 hours for 9 days	Age (mean): 77 years Gender (male to female ratio): 1:5 Spain	confirmed by ventilation-perfusion lung scanning	
Morris 1976[220]	Intervention (n=80): 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. Comparison (n=80) Control group, no prophylaxis. No further details reported	n=160 People admitted to hospital with a fractured neck of femur (sub-capital or intertrochanteric) Age (mean): 78.3 years Gender (male to female ratio): 1:7 UK	All-cause mortality (90 days) DVT (symptomatic and asymptomatic) (10 days): confirmed by I^{125} fibrinogen uptake test and scans PE (time-point not reported): confirmed by clinical signs, chest X-rays and electrocardiograms Major bleeding (time-point not reported): definition not reported	Included in CG92
Moskovitz 1978 [221]	Intervention (n=29): 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. Comparison (n=23): Placebo, saline, subcutaneously given every 8 hour for 7 days. Patients wore	n=52 People admitted for a hip fracture Age: 61% ≥70 years Gender (male to female ratio): 1:2 USA	All-cause mortality (time-point not reported) DVT (symptomatic and asymptomatic) (10 days): confirmed by I^{125} fibrinogen uptake test and scans 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 Major bleeding (time-point not reported): definition not reported Fatal PE (time-point not reported): definition not reported	
Pulmonary Embolism Prevention Collaborative Group 2000: PEP trial [248]	Intervention (n=6679): Aspirin, 160mg, orally once daily, for 35 days 44% also taking UFH or LMWH and 30% also wearing AES Comparison (n=6677): Placebo, orally once daily for 35 days 43% also taking UFH or LMWH and 29% also wearing AES	n=13356 People admitted for a femoral-neck fracture or other fracture of the proximal femur. Age (mean): 79 years Gender (male to female ratio): 1:4 Australia, New Zealand, South Africa, Sweden, UK	All-cause mortality (35 days) PE (35 days): confirmed by pulmonary angiogram, a high-probability ventilation-perfusion scan and at necropsy. Fatal PE (35 days): confirmed by necropsy Wound infection (35 days)	New study Additional heparin and stocking prophylaxis in some people in both the intervention and control groups. 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): Unfractionated heparin, 5000IU, subcutaneously administered three times daily for 14 days. Comparison (n=65): Placebo, given for 14 days.	n=130 People admitted with proximal femoral fractures Age (mean): 73 years Gender (male to female ratio): 1:3 Denmark	All-cause mortality (time-point not reported) 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. 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. Comparison (n=96): Rivaroxaban, 10mg, orally given from 6 hours postoperatively for 28 days Concomitant treatment: All patients were encouraged to perform passive movement training of the affected limbs at day 2 after the surgery.	n=287 People admitted with hip fractures Age (mean): Gender (male to female ratio): 1:1.6 China	All-cause mortality (30 days) DVT (symptomatic and asymptomatic) (30 days): confirmed by colour Doppler ultrasound. Doppler ultrasound was recommended for asymptomatic patients. PE (30 days): confirmed by CT pulmonary angiogram (CTPA) when PE was suspected and/or confirmed. Fatal PE (30 days):	New study
Xabregas 1978[324]	Intervention (n=25): Unfractionated heparin, calcium, adjusted by weight, 100IU/kg,	n=50 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. Comparison (n=25): Placebo, saline solution, given for 14 days.	Age (mean): 76 years Gender (male to female ratio): 1:3 Australia	fibrinogen uptake test and scans PE (time-point not reported): definition not reported 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) 11 days	LOW[a] due to imprecision	(0.55 to 1.97)		(from 10 fewer to 21 more)
Fatal PE	1671 (1 study) 11 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.99 (0.14 to 7.01)	2 per 1000	0 fewer per 1000 (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 (1 study) 30 days	LOW[b] due to imprecision	Peto OR 7.39 (0.15 to 372.38)	0 per 1000	-[a]
DVT (symptomatic and asymptomatic)	192 (1 study) 30 days	VERY LOW[b,c] due to indirectness, imprecision	RR 1.8 (0.63 to 5.17)	52 per 1000	42 more per 1000 (from 19 fewer to 217 more)
PE	192 (1 study) 30 days	LOW[b] due to imprecision	RR 2 (0.18 to 21.69)	10 per 1000	10 more per 1000 (from 9 fewer to 216 more)
Fatal PE	192 (1 study) 30 days	LOW[b] due to imprecision	Peto OR 7.39 (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) 14 days	MODERATE[a] due to risk of bias	(0.38 to 0.73)		(from 102 fewer to 234 fewer)
PE	290 (3 studies) time-point not reported	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.16 (0.4 to 3.38)	35 per 1000	6 more per 1000 (from 21 fewer to 83 more)
Fatal PE	130 (1 study) time-point not reported	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 1 (0.06 to 16.16)	15 per 1000	0 fewer per 1000 (from 14 fewer to 186 more)
Wound infection	150 (2 studies) time-point not reported	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.9 (0.39 to 2.08)	133 per 1000	13 fewer per 1000 (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 (1 study) time-point not reported	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.1 (0.01 to 0.97)	130 per 1000	116 fewer per 1000 (from 3 fewer to 129 fewer)
DVT (symptomatic and	52 (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) 35 days	MODERATE[b] due to indirectness	(0.85 to 1.1)		(from 10 fewer to 7 more)
PE	13356 (1 study) 35 days	LOW[a,b] due to imprecision and indirectness	RR 0.74 (0.45 to 1.2)	6 per 1000	1 fewer per 1000 (from 3 fewer to 1 more)
Fatal PE	13356 (1 study) 35 days	MODERATE[b] due to indirectness	RR 0.42 (0.24 to 0.72)	6 per 1000	4 fewer per 1000 (from 2 fewer to 5 fewer)
Wound infection	13356 (1 study) 35 days	LOW[a,b] due to imprecision and indirectness	RR 1.17 (0.87 to 1.56)	13 per 1000	2 more per 1000 (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 (1 study) 14 days	MODERATE[a] due to risk of bias	Peto OR 0.14 (0.04 to 0.53)	57 per 1000	48 fewer per 1000 (from 26 fewer to 54 fewer)
PE	304 (1 study) 5-10 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.37 (0.07 to 1.78)	38 per 1000	24 fewer per 1000 (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 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 **Population**: Adults admitted for hip fracture surgery in England. **Interventions:** 1. Fondaparinux sodium (2.5 mg subcutaneously) 2.Warfarin variable dose (adjusted to INR range 2 to 3, average dose 4mg/day) 3. LMWH (average of dalteparin 5000 units subcutaneous daily) and enoxaparin (4000 units subcutaneous daily) 4. UFH (5000 units three times daily) 5. IPCD-FID 6.Aspirin (High dose) 7. No prophylaxis	NR	NR	**Incremental net monetary benefit (INMB)** (pa) 1. **Fondaparinux sodium:** £2148 (rank 1) 2. **Warfarin variable dose**: £1830 (rank 2) 3. **LMWH**: 1711 (rank 3) 4. **UFH**: £1465 (rank 4) 5. **IPCD-FID:** £999 (rank 5) 6. **Aspirin (high dose):** £558 (rank 6) 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 **Interventions:** 1. No post discharge prophylaxis (it is not clear whether prophylaxis was given during the initial hospital stay) 2. Post-discharge prophylaxis with fondaparinux for 10 days	NR	NR	**Incremental net monetary benefit (INMB)** (pa) 1. **No prophylaxis**: £0 (rank 2) 2. **Fondaparinux**: £239 (rank 1)	Fondaparinux had 92% probability of being the cost-effective strategy at £20K threshold. 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

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:** • **LMWH[d], starting 6–12 hours after surgery or** • **fondaparinux sodium[e], starting 6 hours after surgery, providing there is low risk of bleeding. [2018]** **1.5.6 Consider pre-operative VTE prophylaxis for people with fragility fractures of the pelvis, hip or proximal femur if surgery is delayed beyond the day after admission. Give the last dose no less than 12 hours before surgery for LMWH[f] or 24 hours before surgery for fondaparinux sodium[g]. [2018]** **1.5.7 Consider intermittent pneumatic compression for people with fragility fractures of the pelvis, hip or proximal femur at the time of admission if pharmacological prophylaxis is contraindicated. Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [2018]**
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?** **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.

	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) and infection (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	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. 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). 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*** 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. 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

	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. 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. Additionally, two studies were identified but were selectively excluded due to the availability of the more applicable models from CG92. 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. 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. 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. 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

	(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. 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. 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.