27 Elective knee replacement surgery

27.1 Introduction

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

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

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

For full details see review protocol in appendix C.

Table 80: PICO characteristics of review question

Population	Adults and young people (16 years and older) undergoing elective knee replacement surgery admitted to and discharged from hospital
Intervention(s)	Mechanical: • Anti-embolism stockings (AES) (above or below knee) • Intermittent pneumatic compression (IPCD) devices (full leg or below knee) • Foot pumps or foot impulse devices (FID) • Electrical stimulation (including Geko devices) • Continuous passive motion (CPM) Pharmacological: • Unfractionated heparin (UFH) (low dose, administered subcutaneously) • Low molecular weight heparin (LMWH), licensed in UK: ○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*) ○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*) ○ tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*) • LMWH, licensed in countries other than UK: ○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily) ○ Certoparin (3000 units daily) ○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily) ○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily) ○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)

	• Vitamin K Antagonists:
	  ○ warfarin (variable dose only)
	  ○ acenocoumarol (all doses)
	  ○ phenindione (all doses)
	• Fondaparinux (all doses)*
	• Apixaban (2.5mg twice daily)
	• Dabigatran (220mg once daily; 150mg once daily - patients with moderate renal impairment, interacting medicines, over 75 years old)
	• Rivaroxaban (10mg once daily)
	• Aspirin (up to 300mg)*
	
	*off-label

Comparison(s)	Compared to: • Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) • No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Standard versus extended duration prophylaxis • Low versus high dose for LMWH • 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 • Surgical site haematoma (up to 45 days from hospital discharge) 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.

27.3 Clinical evidence

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

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

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

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

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 82, Table 83, Table 84, Table 85, Table 86, Table 87, Table 88, Table 89, Table 90, Table 91, Table 92, Table 93, Table 94, Table 95, Table 96, Table 97, Table 98, Table 99, Table 100, Table 101, Table 102, Table 103, Table 104, Table 105, Table 106, Table 107, Table 108, Table 109, Table 110, Table 111, Table 112, Table 113, Table 114, Table 115, Table 116, Table 117 and Table 118). See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

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

Table 81: Summary of studies included in the review

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 82: Clinical evidence summary: LMWH (standard dose; standard duration) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with LMWH (standard dose) (95% CI)
DVT (symptomatic and asymptomatic)	220 (1 studies) 30 days	MODERATE[a] due to risk of bias	RR 0.25 (0.11 to 0.59)	218 per 1000	164 fewer per 1000 (from 89 fewer to 194 fewer)
PE	220 (1 studies) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.00 to 6.82)	9 per 1000	8 fewer more per 1000 (from 9 fewer to 50 more)
Major bleeding	530 (3 studies) 30 days	VERY LOW[a,b,d,f] due to risk of bias, indirectness, imprecision, inconsistency	Peto OR 0.98 (0.24 to 3.95)	15 per 1000	0 fewer per 1000 (from 12 fewer to 42 more)
Wound haematoma	219 (1 study) 8 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.67 (0.48 to 123.42)	0 per 1000	-[d]
Technical complications of mechanical interventions	220 (1 study) time-point not reported	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	Not estimable[e]	Not estimable[e]	0 fewer per 1000 (from 20 fewer to 20 more)[e]
Wound infection	220 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 2.16)	18 per 1000	16 fewer per 1000 (from 18 fewer to 20 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

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

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

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

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

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

Table 83: Clinical evidence summary: LMWH (standard dose; standard duration) versus apixaban

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Apixaban	Risk difference with LMWH (standard dose) (95% CI)
All-cause mortality	3057 (1 study) 60 days	LOW[a] due to imprecision	Peto OR 0.37 (0.05 to 2.61)	2 per 1000	1 fewer per 1000 (from 2 fewer to 3 more)
DVT (symptomatic and asymptomatic)	1968 (1 study) 14 days	MODERATE[b] due to risk of bias	RR 1.67 (1.38 to 2.01)	146 per 1000	98 more per 1000 (from 56 more to 148 more)
PE	3057 (1 study) 14 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.17 (0.02 to 1.38)	4 per 1000	3 fewer per 1000 (from 4 fewer to 1 more)
Major bleeding	3009 (1 study) 14 days	LOW[a] due to imprecision	RR 1.55 (0.67 to 3.57)	6 per 1000	3 more per 1000 (from 2 fewer to 15 more)
Fatal PE	3057 (1 study) 14 days	LOW[a] due to imprecision	Peto OR 0.14 (0 to 6.82)	1 per 1000	1 fewer per 1000 (from 1 fewer to 4 more)
Clinically relevant non-major bleeding	3009 (1 study) 14 days	MODERATE[a] due to imprecision	RR 1.31 (0.89 to 1.93)	29 per 1000	9 more per 1000 (from 3 fewer to 27 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Apixaban	Risk difference with LMWH (standard dose) (95% CI)
Wound haematoma	3009 (1 study) 14 days	LOW[a] due to imprecision	Peto OR 0.13 (0 to 6.79)	1 per 1000	1 fewer per 1000 (from 1 fewer to 4 more)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 84: Clinical evidence summary: LMWH (standard dose; standard duration) versus dabigatran

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

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

a Zero events in both arms of studies included. Risk difference calculated in Review Manager.
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Absolute effects could not be calculated due to zero events in the control

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

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

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

a Absolute effects could not be calculated due to zero events in the control arm
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 86: Clinical evidence summary: LMWH (standard dose; standard duration) versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with LMWH (standard dose) (95% CI)
DVT (symptomatic and asymptomatic)	222 (1 study) 28 days	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.76 (0.4 to 1.46)	164 per 1000	39 fewer per 1000 (from 98 fewer to 75 more)
PE	222 (1 study) 28 days	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]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
d Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

Table 87: Clinical evidence summary: LMWH (standard dose; standard duration) versus AES

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with LMWH (standard dose) (95% CI)
DVT (symptomatic and asymptomatic)	220 (1 study) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.43 (0.17 to 1.07)	127 per 1000	73 fewer per 1000 (from 106 fewer to 9 more)
PE	220 (1 study) 30 days)	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.00 to 6.82)	9 per 1000	8 fewer per 1000 (from 9 fewer to 50 more)
Technical complications of mechanical interventions	220 (1 study) time-point not reported	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	Not estimable[e]	Not estimable[e]	0 fewer per 1000 (from 20 fewer to 20 more)[e]
Wound infection	220 (1 study) 30 days)	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 2.16)	18 per 1000	16 fewer per 1000 (from 18 fewer to 20 more)

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

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

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

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

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

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

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IPCD	Risk difference with LMWH (standard dose) (95% CI)
PE	350 (2 studies) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 20 fewer to 20 more)[c]
Technical complications of mechanical interventions	220 (1 study) time-point not reported	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 20 fewer to 20 more)[e]
Wound infection	220 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.00 to 6.82)	9 per 1000	8 fewer per 1000 (from 9 fewer to 50 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Zero events in both arms. Risk difference calculated in Review Manager.
d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
e Absolute effects could not be calculated due to zero events in the control arm

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

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

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

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Foot pump + AES	Risk difference with LMWH (standard dose) + AES (95% CI)
DVT (symptomatic and asymptomatic)	188 (1 study) 8 days	LOW[a,b] due to risk of bias, imprecision	RR 0.94 (0.73 to 1.21)	576 per 1000	35 fewer per 1000 (from 155 fewer to 121 more)
Fatal PE	188 (1 study) 8 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.15 (0.01 to 2.40)	20 per 1000	17 fewer per 1000 (from 20 fewer to 27 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Absolute effects could not be calculated due to zero events in the control arm

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

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with UFH	Risk difference with LMWH (standard dose) (95% CI)
Wound haematoma	184 (1 study) 7-9 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.68 (0.29 to 1.59)	129 per 1000	41 fewer per 1000 (from 92 fewer to 76 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 92: Clinical evidence summary: LMWH (standard dose; standard duration) + AES versus UFH + AES

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH + AES	Risk difference with LMWH (standard dose) + AES (95% CI)
DVT (symptomatic and asymptomatic)	184 (1 study) 7-9 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.86 (0.52 to 1.42)	269 per 1000	38 fewer per 1000 (from 129 fewer to 113 more)
PE	184 (1 study) 7-9 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 20 fewer to 20 more)[c]
Wound infection	184 (1 study) 7-9 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.34 (0.04 to 3.21)	32 per 1000	21 fewer per 1000 (from 31 fewer to 71 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Zero events in both arms. Risk difference calculated in Review Manager.

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

Outcomes	No of	Quality of the	Relative effect	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	(95% CI)	Risk with LMWH (standard duration)	Risk difference with LMWH (extended duration) (95% CI)
DVT (symptomatic and asymptomatic)	299 (1 study) 27-29 days	LOW[a] due to imprecision	RR 0.83 (0.55 to 1.25)	257 per 1000	44 fewer per 1000 (from 116 fewer to 64 more)
PE	438 (1 study) 27-29 days	LOW[a] due to imprecision	Peto OR 0.14 (0.01 to 2.20)	9 per 1000	8 fewer per 1000 (from 9 fewer to 11 more)
Major bleeding	438 (1 study) 27-29 days	LOW[a] due to imprecision	Peto OR 0.14 (0 to 6.95)	5 per 1000	4 fewer per 1000 (from 5 fewer to 26 more)
Heparin-induced thrombocytopaenia	438 (1 study) 27-29 days	LOW[a] due to imprecision	RR 1.02 (0.14 to 7.17)	9 per 1000	0 more per 1000 (from 8 fewer to 56 more)
a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 94: Clinical evidence summary: LMWH (standard dose; standard duration) + AES versus LMWH (low dose; standard duration) + AES

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (low dose) + AES	Risk difference with LMWH (standard dose) (95% CI) + AES
DVT (symptomatic and asymptomatic)	152 (1 study) 14 days	LOW[a,b] due to risk of bias, imprecision	RR 0.78 (0.52 to 1.16)	436 per 1000	96 fewer per 1000 (from 209 fewer to 70 more)
PE	152 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.05 (0.07 to 16.55)	13 per 1000	1 more per 1000 (from 12 fewer to 199 more)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 95: Clinical evidence summary: LMWH (standard dose; standard duration) + AES versus AES

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with LMWH (standard dose) + AES (95% CI)
DVT (symptomatic and asymptomatic)	153 (1 study) 14 days	LOW[a,b] due to risk of bias, imprecision	RR 0.56 (0.39 to 0.80)	608 per 1000	267 fewer per 1000 (from 122 fewer to 371 fewer)
PE	153 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.07 (0.07 to 16.76)	13 per 1000	1 more per 1000 (from 12 fewer to 199 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 96: Clinical evidence summary: LMWH (standard dose; standard duration) versus LMWH (low dose; standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (low dose)	Risk difference with LMWH (standard dose) (95% CI)
Major bleeding	180 (1 study) 14 days	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 7.23 (0.14 to 364.38)	0 per 1000	-[a]

a Absolute effects could not be calculated due to zero events in the control arm
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 97: Clinical evidence summary: LMWH (standard dose; standard duration) + CPM versus CPM

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

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

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

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

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

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

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

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No pharmacological prophylaxis	Risk difference with LMWH (low dose) (95% CI)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 99: Clinical evidence summary: LMWH (low dose; standard duration) + AES versus AES

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with LMWH (low dose) + AES (95% CI)
DVT (symptomatic and asymptomatic)	157 (1 study) 14 days	LOW[a,b] due to risk of bias, imprecision	RR 0.72 (0.53 to 0.98)	608 per 1000	170 fewer per 1000 (from 12 fewer to 286 fewer)
PE	157 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.01 (0.06 to 15.91)	13 per 1000	0 more per 1000 (from 12 fewer to 189 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 100: Clinical evidence summary: LMWH (high dose; standard duration) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with LMWH (high dose) (95% CI)
All-cause mortality	131 (1 study) 14 days	LOW[b] due to imprecision	Not estimable[a]	Not estimable[a]	0 fewer per 1000 (from 30 fewer to 30 more)[a]
DVT (symptomatic and	129 (1 study)	HIGH	RR 0.29	578 per 1000	410 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with LMWH (high dose) (95% CI)
asymptomatic)	14 days		(0.16 to 0.52)		(from 278 fewer to 486 fewer)
Major bleeding	131 (1 study) 14 days	LOW[b] due to imprecision	Peto OR 0.13 (0 to 6.72)	15 per 1000	13 fewer per 1000 (from 15 fewer to 80 more)

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

Table 101: Clinical evidence summary: LMWH (high dose; standard duration) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH	Risk difference with LMWH (high dose) (95% CI)
DVT (symptomatic and asymptomatic)	288 (1 study) 15 days	LOW[a,b] due to risk of bias, imprecision	RR 0.72 (0.56 to 0.93)	538 per 1000	151 fewer per 1000 (from 38 fewer to 237 fewer)
PE	288 (1 study) 15 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0.00 to 6.73)	7 per 1000	6 fewer per 1000 (from 7 fewer to 38 more)
Major bleeding	453 (1 study) 15 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.99 (0.2 to 4.84)	13 per 1000	0 fewer per 1000 (from 11 fewer to 51 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 102: Clinical evidence summary: LMWH (high dose; standard duration) versus VKA

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with LMWH (high dose) (95% CI)
All-cause mortality	1237 (3 studies) 15 days	LOW[a] due to imprecision	Peto OR 0.37 (0.05 to 2.66)	5 per 1000	3 fewer per 1000 (from 5 fewer to 8 more)
DVT (symptomatic and asymptomatic)	984 (3 studies) 15 days	MODERATE[a] due to imprecision	RR 0.63 (0.53 to 0.75)	438 per 1000	162 fewer per 1000 (from 109 fewer to 206 fewer)
PE	984 (3 studies) 15 days	LOW[a] due to imprecision	Peto OR 0.76 (0.17 to 3.37)	8 per 1000	2 fewer per 1000 (from 7 fewer to 19 more)
Major bleeding	1319 (3 studies) 15 days	LOW[a] due to imprecision	RR 1.61 (0.74 to 3.51)	15 per 1000	9 more per 1000 (from 4 fewer to 38 more)
Fatal PE	218 (1 study) 12±2 days	VERY LOW[a,c] due to risk of bias, imprecision	Not estimable[b]	Not estimable[b]	0 fewer per 1000 (from 20 fewer to 20 more)[b]
Wound haematoma	670 (1 study) 14 days	LOW[a] due to imprecision	RR 0.99 (0.06 to 15.83)	3 per 1000	0 fewer per 1000 (from 3 fewer to 44 more)
Wound infection	300 (1 study) 12±2 days	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.34 (0.04 to 3.21)	20 per 1000	13 fewer per 1000 (from 19 fewer to 44 more)

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

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

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

Table 103: Clinical evidence summary: LMWH (high dose; standard duration) versus fondaparinux

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fondaparinux	Risk difference with LMWH (high dose) (95% CI)
Major bleeding	1034 (1 study) 49 days	LOW[a,b] due to risk of bias, indirectness	RR 0.09 (0.01 to 0.70)	21 per 1000	19 fewer per 1000 (from 6 fewer to 21 fewer)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

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

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

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Zero events in both arms. Risk difference calculated in Review Manager.

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

Table 105: Clinical evidence summary: LMWH (high dose; standard duration) versus apixaban

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Apixaban	Risk difference with LMWH (high dose) (95% CI)
All-cause mortality	3485 (2 studies) 60 days	LOW[a] due to imprecision	RR 1.68 (0.48 to 5.79)	2 per 1000	2 more per 1000 (from 1 fewer to 11 more)
DVT (symptomatic and asymptomatic)	2581 (2 studies) 14 days	MODERATE[a] due to imprecision	RR 1.10 (0.85 to 1.41)	81 per 1000	8 more per 1000 (from 12 fewer to 33 more)
PE	3512 (2 studies) 14 days	LOW[a,b] due to imprecision, inconsistency	RR 0.87 (0.42 to 1.78)	8 per 1000	1 fewer per 1000 (from 5 fewer to 6 more)
Major bleeding	3638 (2 studies) 14 days	LOW[a,b] due to imprecision, inconsistency	RR 1.63 (0.83 to 3.19)	8 per 1000	5 more per 1000 (from 1 fewer to 17 more)
Fatal PE	3195 (2 studies) 14 days	LOW[a] due to imprecision	Peto OR 0.14 (0.01 to 2.17)	1 per 1000	1 fewer per 1000 (from 1 fewer to 1 more)
Clinically relevant non-major bleeding	3184 (1 study) 14 days	MODERATE[a] due to imprecision	RR 1.35 (0.88 to 2.08)	22 per 1000	8 more per 1000 (from 3 fewer to 24 more)
Wound infection	454 (1 study)	LOW[a] due to imprecision	RR 0.34 (0.04 to	20 per 1000	13 fewer per 1000 (from 19 fewer to 36 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Apixaban	Risk difference with LMWH (high dose) (95% CI)
	14 days		2.81)		

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

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

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

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

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

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

Table 107: Clinical evidence summary: LMWH (high dose; standard duration) versus rivaroxaban

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

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

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

Table 108: Clinical evidence summary: Fondaparinux versus no pharmacological prophylaxis

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with No pharmacological prophylaxis	Risk difference with Fondaparinux (95% CI)
Major bleeding	171 (1 study) 11-17 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.04 (0.07 to 16.29)	11 per 1000	0 more per 1000 (from 11 fewer to 176 more)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 109: Clinical evidence summary: Fondaparinux + AES versus AES

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

a Zero events in both arms. Risk difference calculated in Review Manager.
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 110: Clinical evidence summary: Fondaparinux + IPCD + AES versus VKA + IPCD + AES

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA + IPCD + AES	Risk difference with Fondaparinux + IPCD + AES (95% CI)
All-cause mortality	118 (1 study) 30 days	VERY LOW[b,c] due to risk of bias, imprecision	Not estimable[a]	Not estimable[a]	0 fewer per 1000 (from 30 fewer to 30 more)[a]
DVT (symptomatic and asymptomatic)	118 (1 study) 30 days	VERY LOW[b,c] due to risk of bias, imprecision	Not estimable[a]	Not estimable[a]	0 fewer per 1000 (from 30 fewer to 30 more)[a]
PE	118 (1 study) 30 days	VERY LOW[b,c] due to risk of bias, imprecision	Not estimable[a]	Not estimable[a]	0 fewer per 1000 (from 30 fewer to 30 more)[a]

a Zero events in both arms. Risk difference calculated in Review Manager.
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 111: Clinical evidence summary: Apixaban versus VKA

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with Apixaban (95% CI)
	14 days	imprecision			
Major bleeding	456 (1 study) 14 days	LOW[b] due to imprecision	Peto OR 4.50 (0.56 to 36.39)	0 per 1000	-[d]
Fatal PE	317 (1 study) 7 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 4.59 (0.07 to 284.39)	0 per 1000	-[d]
Wound infection	456 (1 study) 14 days	LOW[b] due to imprecision	RR 0.99 (0.25 to 3.90)	20 per 1000	0 fewer per 1000 (from 15 fewer to 58 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Zero events in both arms. Risk difference calculated in Review Manager.
d Absolute effects could not be calculated due to zero events in the control arm.

Table 112: Clinical evidence summary: Dabigatran versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with Dabigatran (95% CI)
All-cause mortality	253 (1 study) 14 days	LOW[b] due to imprecision	Not estimable[a]	Not estimable[a]	0 fewer per 1000 (from 20 fewer to 20 more)[a]
DVT (symptomatic and asymptomatic)	197 (1 study) 14 days	MODERATE[c] due to risk of bias	RR 0.42 (0.29 to 0.63)	564 per 1000	327 fewer per 1000 (from 209 fewer to 401 fewer)
PE	253	LOW[b]	Not	Not estimable[a]	0 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with Dabigatran (95% CI)
	(1 study) 14 days	due to imprecision	estimable[a]		(from 20 fewer to 20 more)[a]
Major bleeding	253 (1 study) 14 days	LOW[b] due to imprecision	Peto OR 2.64 (0.37 to 19.00)	8 per 1000	13 more per 1000 (from 5 fewer to 126 more)
Clinically relevant non-major bleeding	253 (1 study) 14 days	LOW[b] due to imprecision	RR 0.64 (0.11 to 3.77)	24 per 1000	9 fewer per 1000 (from 22 fewer to 67 more)

a Zero events in both arms. Risk difference calculated in Review Manager.
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 113: Clinical evidence summary: Rivaroxaban versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with Rivaroxaban (95% CI)
DVT (symptomatic and asymptomatic)	212 (1 study) 28 days	HIGH	RR 0.18 (0.05 to 0.59)	164 per 1000	134 fewer per 1000 (from 67 fewer to 155 fewer)
PE	212 (1 study) 28 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	Not estimable[b]	Not estimable[b]	0 fewer per 1000 (from 20 fewer to 20 more)[b]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Zero events in both arms. Risk difference calculated in Review Manager.
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with Rivaroxaban (95% CI)
d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 114: Clinical evidence summary: Foot pump versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with Foot pump (95% CI)
DVT (symptomatic and asymptomatic)	60 (1 study) 10 days	MODERATE[a] due to risk of bias	RR 0.3 (0.13 to 0.7)	594 per 1000	416 fewer per 1000 (from 178 fewer to 517 fewer)
PE	60 (1 study) time-point not reported	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	Not estimable[b]	Not estimable[b]	0 fewer per 1000 (from 60 fewer to 60 more)[b]
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Zero events in both arms. Risk difference calculated in Review Manager. c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 115: Clinical evidence summary: AES versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with AES (95% CI)
DVT (symptomatic and asymptomatic)	220 (1 study) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.58 (0.32 to 1.07)	218 per 1000	92 fewer per 1000 (from 148 fewer to 15 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with AES (95% CI)
PE	220 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.00 (0.06 to 16.09)	9 per 1000	0 fewer per 1000 (from 9 fewer to 120 more)
Major bleeding	220 (1 study) time-point not reported	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 20 fewer to 20 more)[c]
Technical complications of mechanical interventions	220 (1 study) time-point not reported	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 20 fewer to 20 more)[c]
Wound infection	220 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.00 (0.14 to 6.97)	18 per 1000	0 fewer per 1000 (from 16 fewer to 96 more)

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

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

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

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

Table 116: Clinical evidence summary: IPCD versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with IPCD (95% CI)
DVT (symptomatic and asymptomatic)	220 (1 study) 7 days	LOW[a,b] due to risk of bias, imprecision	RR 0.38 (0.18 to 0.77)	218 per 1000	135 fewer per 1000 (from 50 fewer to 179 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with IPCD (95% CI)
PE	220 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.00 to 6.82)	9 per 1000	8 fewer per 1000 (from 9 fewer to 50 more)
Major bleeding	220 (1 study) time-point not reported	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 20 fewer to 20 more)[c]
Technical complications of mechanical interventions	220 (1 study) time-point not reported	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 20 fewer to 20 more)[c]
Wound infection	220 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.51 (0.14 to 6.97)	18 per 1000	9 fewer per 1000 (from 17 fewer to 66 more)

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

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

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

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

Table 117: Clinical evidence summary: IPCD versus AES

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with IPCD (95% CI)
DVT (symptomatic and asymptomatic)	220 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.64 (0.29 to 1.42)	127 per 1000	46 fewer per 1000 (from 90 fewer to 53 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with IPCD (95% CI)
PE	220 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.00 to 6.82)	9 per 1000	8 fewer per 1000 (from 9 fewer to 50 more)
Major bleeding	220 (1 study) time-point not reported	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 20 fewer to 20 more)[c]
Technical complications of mechanical interventions	220 (1 study) time-point not reported	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 20 fewer to 20 more)[c]
Wound infection	220 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.51 (0.05 to 4.96)	18 per 1000	9 fewer per 1000 (from 17 fewer to 66 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Zero events in both arms. Risk difference calculated in Review Manager.
d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 118: Clinical evidence summary: CPM versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with CPM (95% CI)
DVT (symptomatic and asymptomatic)	65 (1 study) 90 days	VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	Not estimable[a]	Not estimable[a]	0 fewer per 1000 (from 60 fewer to 60 more)[a]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with CPM (95% CI)

a Zero events in both arms. Risk difference calculated in Review Manager.
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

27.4 Economic evidence

Published literature

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

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

New cost-effectiveness analysis

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

Model overview

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

Population

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

Comparators

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

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

Model structure

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

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

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

Model inputs

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

Sensitivity analysis

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

Table 119: One-way sensitivity analyses

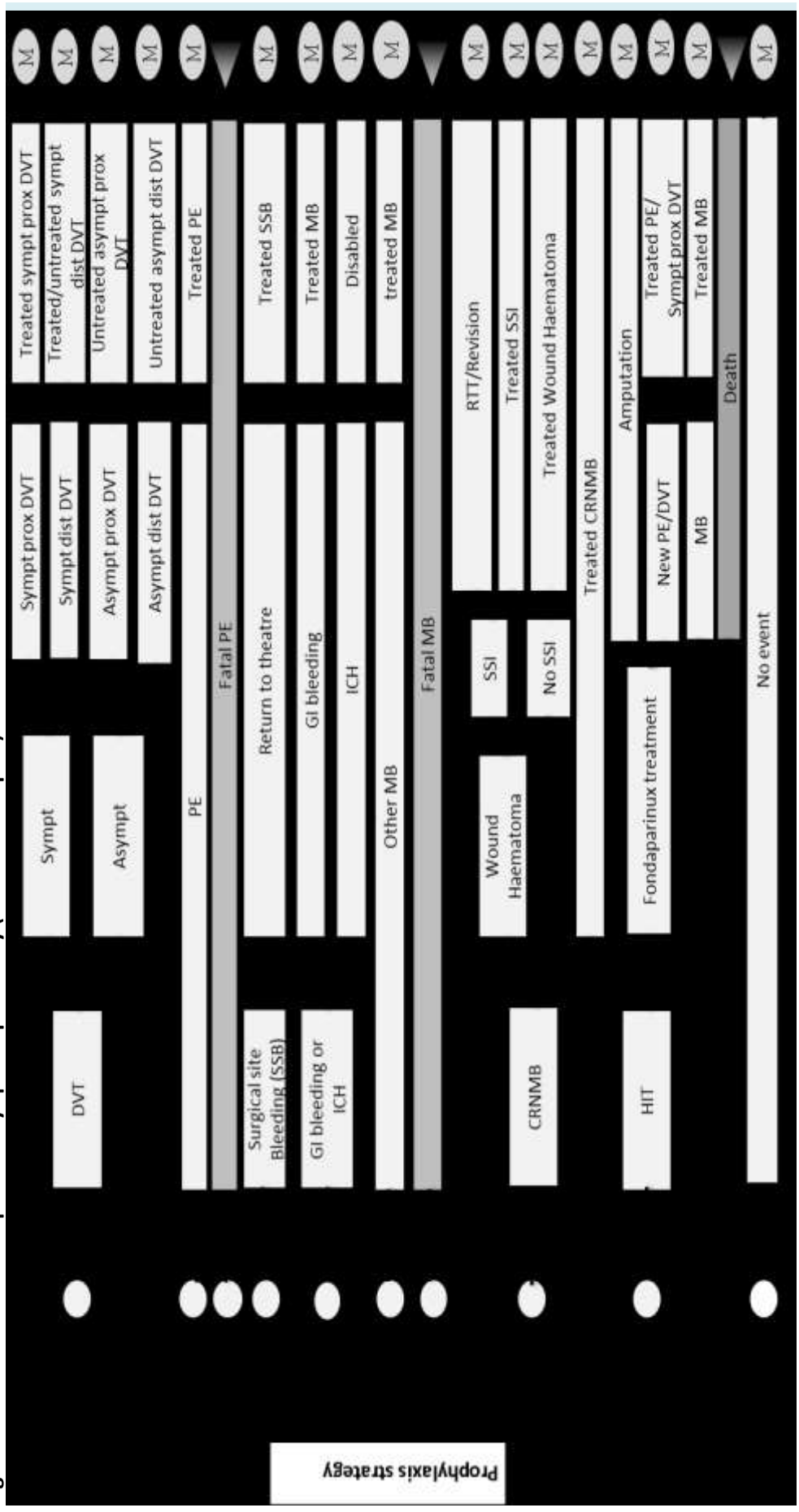
	description	Base case input value	Alternative value for sensitivity analysis
SA1	Cost effectiveness threshold	£20,000	£30,000
SA2	Discount rate for costs and QALYs	3.5%	1.5%
SA3	Prophylaxis duration	Based on the RCTs included in the DVT NMA	based on summary of product characteristics (SmPC)
SA4	Cohort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

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

(a) Source: National Joint Registry[36]

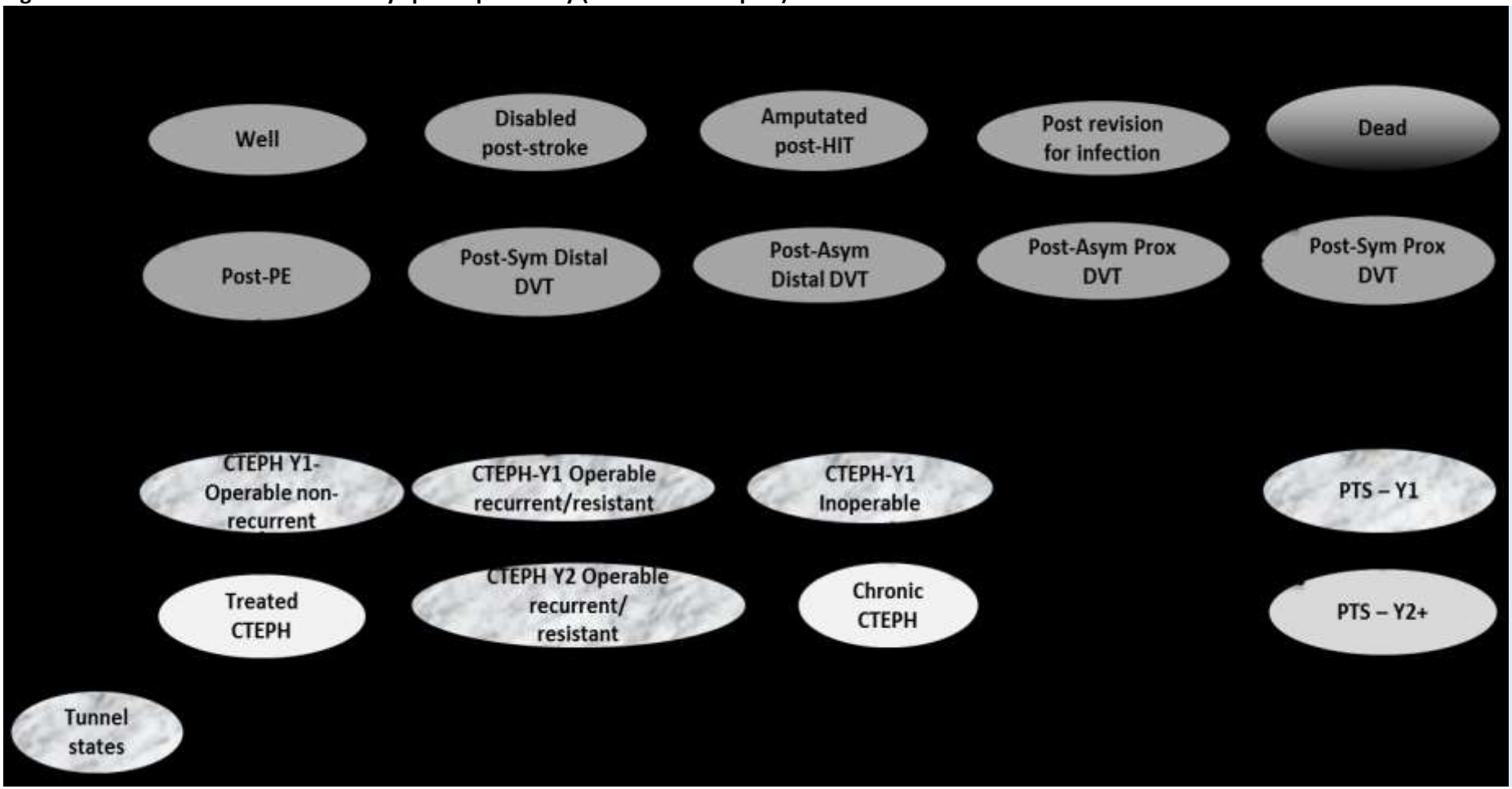
(b) Source: ONS [237]

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



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

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



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

Results

Base case

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

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

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

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

Sensitivity analysis

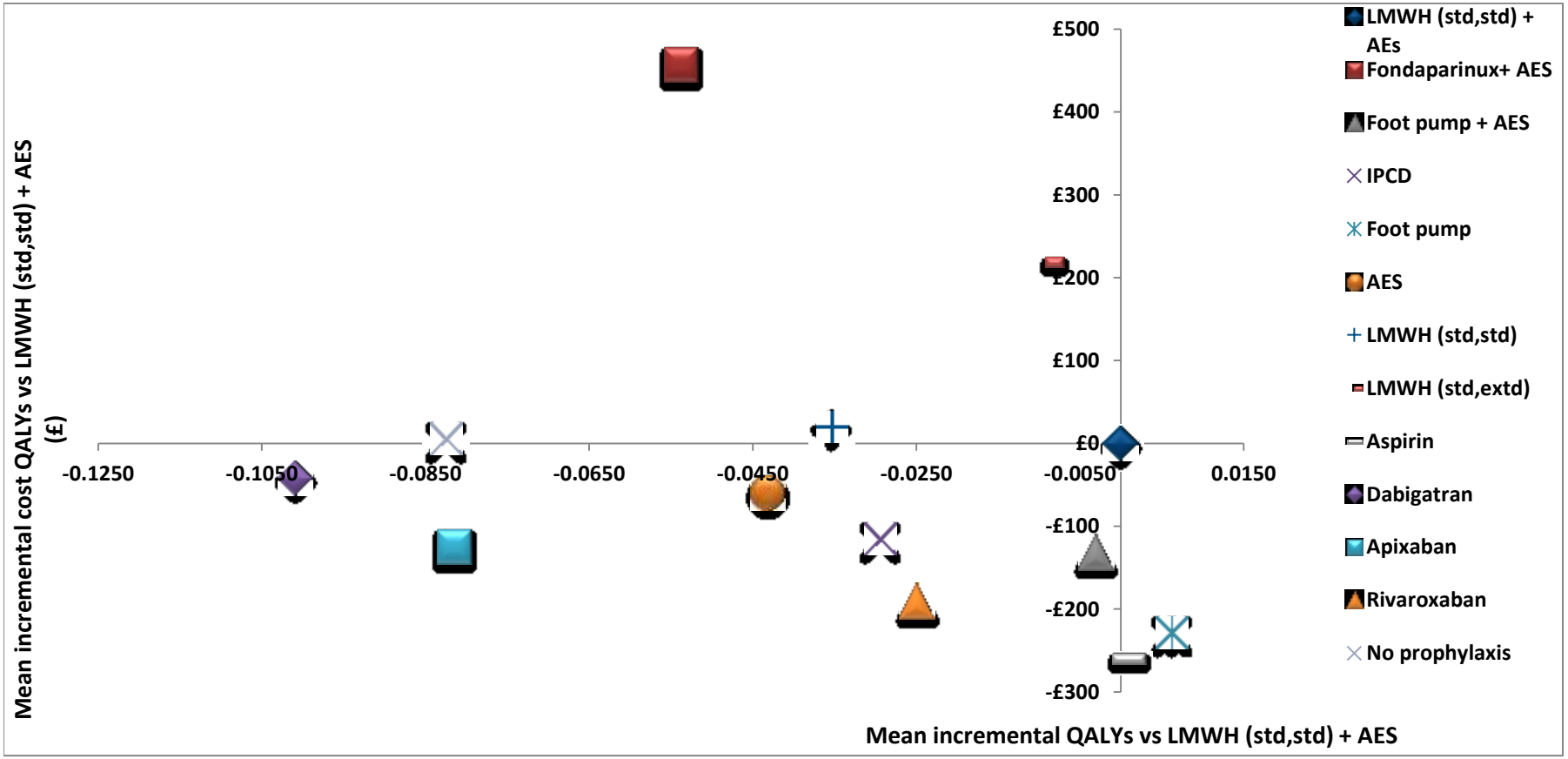
In all the SAs undertaken, the most cost effective option (foot pump) and the ranking of all interventions remained largely the same.

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

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

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

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



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

Discussion

Interpretation and limitations

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

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

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

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

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

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

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

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

Generalisability to other populations/settings

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

Conclusions

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

27.5 Evidence statements

Clinical

Pairwise meta-analysis statements

Pharmacological interventions versus pharmacological interventions

LMWH (standard dose; standard duration)

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

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

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

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

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

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

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

LMWH (standard dose; extended duration)

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

LMWH (low dose; standard duration)

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

LMWH (high dose; standard duration)

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

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

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

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

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

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

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

Fondaparinux

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

Apixaban

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

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

Dabigatran

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

Rivaroxaban

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

Pharmacological interventions versus mechanical interventions

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

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

Combination interventions versus single interventions

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

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

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

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

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

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

Combination interventions versus combination interventions

LMWH (standard dose; standard duration) + AES

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

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

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

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

LMWH (high dose; standard duration) + AES

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

Fondaparinux + IPCD + AES

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

Mechanical interventions versus mechanical interventions

Foot pump

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

AES

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

IPCD

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

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

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

Continuous passive motion

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

Network meta-analysis statements

DVT (symptomatic and asymptomatic)

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

PE

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

Major bleeding

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

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

Economic

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

27.6 Recommendations and link to evidence

Recommendations	**1.5.11 Offer VTE prophylaxis to people undergoing elective knee replacement surgery whose VTE risk outweighs their risk of bleeding. Choose any one of:** • **aspirin[n] (75 or 150 mg) for 14 days** • **LMWH[o] for 14 days combined with anti-embolism stockings until discharge** • **Rivaroxaban[p]. Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (NICE technology appraisal guidance 170).] [2018]** **1.5.12 Consider one of the following if none of the options in recommendation 1.5.11 can be used:** • **Apixaban[q] is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement**

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

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

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

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

	surgery. [This text is from Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (NICE technology appraisal guidance 245).] • **Dabigatran etexilate[r], within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (NICE technology appraisal guidance 157).]** **1.5.13 Consider intermittent pneumatic compression if pharmacological prophylaxis is contraindicated in people undergoing elective knee replacement surgery. Continue until the person is mobile. [2018]**
Research recommendation	**None**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge), pulmonary embolism (7-90 days from hospital discharge), fatal PE (7-90 days from hospital discharge), major bleeding (up to 45 days from hospital discharge) and surgical site haematoma (up to 45 days from hospital discharge) as critical outcomes. 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. Three network meta-analyses were conducted for this population, evaluating the outcomes DVT (symptomatic and asymptomatic), PE and major bleeding across numerous interventions. Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	Evidence from direct pairwise comparisons was included in the network meta-analyses for the elective knee replacement population. The quality of the pairwise comparisons ranged from very low to high due to risk of bias, imprecision, indirectness and inconsistency. The DVT (symptomatic and asymptomatic) network evaluated 19 interventions, the PE network evaluated 13 interventions and major bleeding network evaluated 11 interventions. Inconsistencies were identified in the DVT (symptomatic and asymptomatic) and PE networks between the direct pairwise evidence and the NMA evidence but there was good calibration for all the outcomes with small differences between the residual deviance and DIC values for the network meta-analysis models that were ran. Very wide credible intervals around the median network meta-analyses values present some uncertainty around the NMA results, particularly for

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

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

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

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

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

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

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

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

	options could only be considered if all the three recommended options are not suitable for the person (for example due to contraindications or issues related to patient preference). For those with contraindications for pharmacological prophylaxis, the committee and the orthopaedic subgroup considered that foot pump/IPCD appeared to be more cost-effective in this population compared to AES. This was in line with the evidence from other populations where AES tended to be less effective than previously thought. The committee also noted the difficulty in using AES in this specific population where application is only possible on the opposite leg. Given the very large cost impact of using AES in this population, the considerable time required for nurses to fit them and the considerable uncertainty about their effectiveness; the committee and the subgroup considered that the use of AES as a sole prophylaxis option in this population should be discouraged. However, AES still ranked higher than no prophylaxis and the committee therefore determined there was not enough evidence to recommend against their use as a sole means of prophylaxis. The committee also noted that in general it was not possible to include any side effects for the mechanical prophylaxis options in the model, and hence their cost effectiveness might be over-estimated. Additionally, the trials of all mechanical prophylaxis options have used them for longer durations than how they are currently used in practice, where early mobilisation is encouraged, so the efficacy levels seen in the trials may not be possible to replicate in practice. Hence, a weaker “consider” recommendation would be more appropriate.
Other considerations	The committee noted the dose used for aspirin in the evidence represented a non-standard dose for the UK at 100mg per day. Clinicians can decide whether to use 75mg or 150mg.