35 Abdominal surgery (excluding bariatric surgery)

35.1 Introduction

This section covers major abdominal surgery, including both open and laparoscopic surgery. Major abdominal surgery covers inpatients undergoing gastrointestinal, gynaecological and urological surgery.

Gastrointestinal surgery by its nature is heterogeneous in terms of the age of patients, the pathological conditions being dealt with and organs and systems operated upon. There remain a variety of procedures retained within this category that are specialisations in themselves. These include upper gastrointestinal surgery and lower intestinal surgery (or coloproctology). Factors that may alter the risk of VTE:

- Patients having surgery for cancer will have an increased risk of developing a DVT or pulmonary embolism.
- Patients having emergency procedures are often elderly and will consequently be at higher risk of developing a DVT or pulmonary embolism.
- Some patients having emergency procedures may already be using anticoagulation or antiplatelet therapy. This needs to be considered when deciding on the method of VTE prophylaxis.

Open gynaecological surgery includes abdominal and vaginal surgery, excluding caesarean section. Factors that may alter the risk of VTE:

- Patients may be using hormonal contraception and hormone replacement therapy, which will increase their risk of developing a DVT or pulmonary embolism.
- Patients having surgery for cancer will have an increased risk of developing a DVT or pulmonary embolism.

Open urological surgery is divided into two major groups: pelvic cancer surgery and renal surgery. Patients undergoing these procedures are usually between the ages of 65 and 75.

Factors that may alter the risk of VTE:

- Many urological surgery patients have spinal and epidural anaesthesia. This may reduce the risk of developing a DVT.
- Renal surgery procedures may involve division of the renal vein where it drains into the inferior vena cava. This could potentially increase the risk of VTE.

There are no specific factors that increase the risk of bleeding or the hazard associated with it in open gastrointestinal, gynaecological or urological surgery. There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in these surgeries.

Laparoscopic surgery is used in gastrointestinal, gynaecological and urological surgery. Specific considerations apply to it in all these specialities. Factors that may alter the risk of VTE:

- There is some concern that the increased pressure in the peritoneal cavity during laparoscopic surgery causes venous stasis which may increase VTE risk.
- Some laparoscopic procedures tend to last longer than open procedures.
- Being less invasive, most people will make a quicker return to mobility following laparoscopic procedures compared to open procedures.

Factors that may alter the risk of bleeding:

- Laparoscopic procedures may be associated with less bleeding than open surgery.

- Bleeding may make laparoscopic surgery difficult or impossible and result in the need for conversion to open surgery.

There are no other special factors that may affect the choice, and use of, specific methods of VTE prophylaxis in laparoscopic surgery.

35.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing abdominal surgery (gastrointestinal, gynaecological, urological)?

For full details see review protocol in appendix C.

Table 167: PICO characteristics of review question

Population	Adults and young people (16 years and older) undergoing abdominal surgery (including gastrointestinal, gynaecological, urological) who are admitted to hospital, and outpatients post-discharge
Interventions	Mechanical: • Anti-embolism stockings (AES) (above or below knee) • Intermittent pneumatic compression (IPCD) devices (full leg or below knee) • Foot pumps or foot impulse devices (FID) • Electrical stimulation (including Geko devices) • Continuous passive motion Pharmacological (no minimum duration): • Unfractionated heparin (UFH) (low dose, administered subcutaneously) • Low molecular weight heparin (LMWH), licensed in UK: • 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), acenocoumarol (all doses), phenindione (all doses) • Fondaparinux (all doses) • Apixaban (all doses) • Dabigatran (all doses)

	• Rivaroxaban (all doses) • Aspirin (up to 300mg)* *off-licence
Comparisons	Compared to: • Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) • No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge • 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) (NMA outcome) • Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) (NMA outcome) • Pulmonary embolism (7- 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE (NMA outcome) • Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event (NMA outcome) • Fatal PE (up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE Important outcomes: • Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy • Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) • Heparin-induced thrombocytopaenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.

35.3 Clinical evidence

Sixty-seven studies in 69 papers were included in the review these are summarised in Table 168 below. Sixty-two studies were previously included in the previous guideline (CG92);[5, 317, 316, 292, 293, 6, 19, 37, 38, 44, 29, 30, 28, 25 ,26, 24, 22, 42, 50, 54, 56, 55 ,57 ,58, 92, 102, 109 ,110, 118, 120 ,131 ,138, 136, 156, 160, 159, 169, 175-177, 193, 202, 204, 210,

[232, 235, 238, 239, 236, 245, 250, 251, 268, 272, 284, 286, 291, 290, 294, 303, 137 ,302] and five studies were added to the update; [111, 260, 223, 158, 273, 137]. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 169, Table 170, Table 171, Table 172, Table 173, Table 174, Table 175, Table 176, Table 177, Table 178, Table 179, Table 180, Table 181, Table 182, Table 183, Table 184, Table 185, Table 186, Table 187, Table 188, Table 189, Table 190, Table 191, Table 192, Table 193, Table 194, Table 195, Table 196, Table 197, Table 198, Table 199, Table 200, Table 201, Table 202, Table 203, Table 204, Table 205, Table 206, Table 207). See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

Based on the current review protocol, six systematic reviews that were included in CG92 were excluded but checked for references. The studies from all of one systematic review[11] were excluded due to having the incorrect intervention. Some of the studies from five systematic reviews[7, 61, 167, 217, 256] were excluded due to having incorrect population, intervention or comparisons. For this update, data from the original papers, rather than systematic review data, was used.

A large amount of people undergo major abdominal surgery, and where evidence for other populations relating to torso surgery (e.g. thoracic surgery and cardiac surgery) is lacking, the committee agreed to consider major abdominal surgery as indirect evidence. Therefore in order to compare the clinical effectiveness data of multiple possible interventions, it was proposed that a network meta-analysis be carried out on the outcome data for DVT, PE and major bleeding in this population. These analyses provide estimates of effect (with 95% credible intervals) for each intervention compared to one another and compared to a single baseline risk (in this case the baseline treatment was no prophylaxis or in the case of the major bleeding outcome a combination of no prophylaxis and mechanical prophylaxis). These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. For full details on the NMA methodology and results, please see appendix M.

Table 168: Summary of systematic reviews included in the review

Included studies	Intervention and comparison	Population	Outcomes	Comments
Agnelli 2005[1]	Intervention (n=1433): Fondaparinux (2.5 mg, 1 x daily). Duration: started 6 hours post-op and repeated daily for 5-9 days. Comparison (n=1425): LMWH, standard dose, (dalteparin, 5000U, 1 x daily). Duration: started 2 hours before operation (2500U), and then given 12 hours later (2500U). 5000 units given once daily thereafter for 5-9 days.	n=2858 People having high risk abdominal surgery (duration >45 minutes) Age >40 years Male and female (1584:629) Cancer 67.9% Multiple countries (131 hospitals in 22 countries)	All-cause mortality (32 days) DVT (32 days): confirmed by bilateral venography Symptomatic pulmonary embolism (32 days): confirmed by high probability lung scan, pulmonary angiography, helical computed tomography or autopsy Major bleeding (7-11 days): fatal, retroperitoneal,	

Included studies	Intervention and comparison	Population	Outcomes	Comments
			intracranial, intraspinal, or involved any other critical organ, bleeding leading to reoperation or intervention, or a bleeding index of 2.0 or more Fatal PE (32 days): confirmed by autopsy	
Allan 1983[5]	Intervention (n=97): AES, length not stated. Duration: evening before operation until 7 days post-op Comparison (n=103): no VTE prophylaxis	n=200 People having abdominal surgery (duration >30 minutes) Age >40 years Male and female UK	DVT (7 days): confirmed by fibrinogen uptake test	
Allen 1978[6]	Intervention (n=30): UFH (5000U 2 x daily) Duration: started 2 hours before surgery, until discharge Comparison (n=30): No VTE prophylaxis	n=60 People undergoing urologic surgery (transurethral prostatectomy) Age (average): intervention 71.9, comparison 71.2 UK	All-cause mortality (time-point not reported) Major bleeding (time-point not reported): defined as requiring a transfusion of two units of blood	
Bejjani 1983[19]	Intervention (n=17): UFH (5000U 2 x daily) Duration: started 3 hours before surgery or on admission, for 2 days Comparison (n=17): No VTE prophylaxis (placebo, 2ml saline 2 x daily). Duration: started 3 hours before surgery or on admission, for 2 days	n=34 People undergoing urologic surgery Cancer = 38% United States	PE (postoperatively): confirmed by ventilation perfusion lung scan Major bleeding (postoperatively): defined as bleeding requiring a transfusion of 2 units	
Bergqvist	Intervention (n=46):	n=97	All-cause mortality	

Included studies	Intervention and comparison	Population	Outcomes	Comments
1980[29]	UFH (5000U, 2 x daily) Duration: started 2 hours before surgery or on admission, for 5 days Comparison (n=51): No VTE prophylaxis	People having general surgery (abdominal surgery 56.7%, urologic surgery 38.1%) Male and female (63:34) Age >51 years 22% malignant disease Sweden	(up to 7 days) DVT (up to 7 days): confirmed by I-fibrinogen test Fatal PE (up to 7 days): method of confirmation not reported	
Bergqvist 1986 [25,26]	Intervention (n=215): LMWH, standard dose (dalteparin, 5000U, 1 x daily) Duration: started 2 hours before operation, for 5-7 days Comparison (n=217): UFH 5000U 2 x daily Duration: started 2 hours before operation, for 5-7 days	n=432 People having general surgery (gastric surgery 7.9%, biliary tract surgery 29.6% , colonic surgery 37%, rectal surgery 18.2%, pancreatic surgery 0.5%, other 6.7%) Age > 40 45% malignancies Sweden	All-cause mortality (30 days) DVT (7 days): confirmed by I-labelled fibrinogen uptake test Major bleeding (30 days): defined as bleeding requiring reintervention	
Bergqvist 1988[30]	Intervention (n=505): LMWH, standard dose (dalteparin 5000U, 1 x daily). Duration: started the evening before surgery, for 5-8 days Comparison (n=497): UFH (5000U), 2 x daily (the first injection contained placebo) Duration: started the evening before surgery, for 5-8 days	n=1002 People having general abdominal surgery (gastric surgery 10%, biliary tract surgery 8.6% , colonic surgery 56.6%, rectal surgery 17.6%, pancreatic surgery 2.4%, other 4.6%) Median duration: LMWH = 120 minutes, UFH = 125 minutes Aged > 41 years Male and female (488:514) Sweden	All-cause mortality (30 days) DVT (7 days days): confirmed by I-labelled fibrinogen uptake test PE (30 days): confirmed by scintigraphy Fatal PE (30 days): confirmed by autopsy	
Bergqvist 1995[24]	Intervention (n=1036): LMWH, standard dose, (dalteparin, 5000U, 1 x	n=2070 People having abdominal	All-cause mortality (30 days post op): confirmed by autopsy	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	daily). Duration: started 22 hours the day before surgery for 7 days postoperatively. <u>Comparison (n=1034):</u> LMWH, low dose (dalteparin, 2500U, 1 x daily). Duration: started 22 hours the day before surgery for 7 days postoperatively.	surgery (duration, median: intervention 125 minutes, comparison 129 minutes) Age > 40 years Male and female (985:1085) Sweden	DVT (7 days post-op): confirmed by fibrinogen uptake test PE (30 days): confirmed by perfusion/ ventilation scintigraphy Major bleeding (30 days post-op): defined as those leading to death or reoperation, or as being intracranial, intraocular or intraspinal	
Bergqvist 1996 [28]	<u>Intervention (n=39):</u> LMWH, standard dose (tinzaparin 3500U, 1 x daily). Duration: started post-operatively for >5 days <u>Comparison (n=41):</u> No VTE prophylaxis (placebo)	n=80 People having emergency abdominal surgery Age >40 years Males and females (37:43) 13.8% malignant disease Sweden	All-cause mortality (30 days) DVT (30 days): confirmed by FUT and venography PE (30 days): method of confirmation not reported Major bleeding (30 days): defined as bleeding requiring re-operation, transfusion or other intervention, leading to death or intraocular, intracranial or intraspinal bleeding	
Bergqvist 2002[21]	<u>Intervention (n=253):</u> extended LMWH, standard dose, (enoxaparin, 40mg, 1 x daily). Duration: started 10-14 hours before operation, then once daily for 25-31 days. <u>Comparison (n=248):</u>	n=501 People having abdominal surgery for cancer Duration >45 minutes Age >40 years Male and female (200:132)	All-cause mortality (2 months) DVT (25-31 days): confirmed by bilateral venography PE (3 months): confirmed by V/Q	AES were allowed

Included studies	Intervention and comparison	Population	Outcomes	Comments
	standard LMWH, standard dose, (enoxaparin, 40mg 1 x daily). Duration: started 10-14 hours before operation, then once daily for 6-10 days. Placebo for further 19-21 days.	Cancer 100% Multiple countries	scan or angiogram Major bleeding (3 months): bleeding resulting in death, a decrease in the haemoglobin concentration of 2 g per deciliter or more, or the transfusion of at least 2 units of blood; retroperitoneal, intracranial, or intraocular; resulted in a serious or life-threatening clinical event; or if surgical or medical intervention was required Fatal PE (3 months): confirmed by autopsy	
Borstad 1988[37]	Intervention (n=105): LMWH, standard dose (dalteparin 5000U, 1 x daily) Duration: started 1 hour preoperatively for 7 days Comparison (n=110): UFH (5000U, 2 x daily) Duration: started 1 hour preoperatively for 7 days	n= 215 People having major gynaecological surgery (laparotomy 52.6%, colposuspension 19.6%, vaginal repair 25.1%) Duration >30 minutes Age >40 years Cancer 6% Norway	DVT (7 days): confirmed by plethysmography and venography PE (7 days): confirmed by clinical examination Major bleeding (time-point not reported): defined as if the patient was reoperated, received blood transfusions or had prophylaxis stopped due to bleeding	
Borstad 1992[38]	Intervention (n=77): LMWH, low dose (dalteparin, 2500U, 1 x daily). Duration: started 1 hour before surgery for 7 days	n=152 People having major gynaecological surgery (laparotomy, colposuspension, vaginal repair)	All-cause mortality (1 month) PE (1 month): confirmed by venography if	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=75): UFH (5000U 2 x daily). Duration: started 1 hour before surgery for 7 days	Duration > 30 minutes Age > 40 years Norway	thromboembolic complications suspected from clinical examination Major bleeding (5 days): defined as prophylaxis stopped because of bleeding, transfusions received, perioperative bleeding more than 1000 ml and pelvic haematoma	
Butson 1981[42]	Intervention (n=62): IPCD, knee length Duration: started immediately after anaesthesia and continued until fully ambulant (usually for 24-48 hours) Comparison (n=57): No VTE prophylaxis	n=119 People having general abdominal surgery Age >20 years Males and females (52:67) Canada	DVT (discharge or 14 days): confirmed by fibrinogen scanning, venography, or autopsy Fatal PE (discharge or 14-90 days): confirmed by autopsy	
Caen 1988[44]	Intervention (n=195): LMWH, low dose (dalteparin, 2500U, 1 x daily) Duration: 2 hours before operation until 7 days post-op Comparison (n=190): UFH (5000U, 2 x daily) Duration: 2 hours before operation until 7 days post-op	n=385 People having major abdominal surgery Duration of surgery >30 minutes Age >40 years Males and females (188:197) France	All-cause mortality (30 days) DVT (30 days): confirmed by I-fibrinogen uptake test PE (30 days): method of confirmation not reported Fatal PE (30 days): method of confirmation not reported	
Caprini 1983[48]	Intervention (n=38): • AES, above knee • IPCD, full leg Duration: all patients wore bilateral AES preoperatively. IPCD was then applied prior to the onset of	n=77 People having general surgery (abdominal 64.9, orthopaedic 13%, neurologic 10.4%, genitourinary 10.4%, thoracic 1.3%)	DVT (time-point not reported):confirmed by venography, plethysmography and Doppler PE (time-point not reported):	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	anaesthesia and maintained for at least 3 days postoperatively or until ambulant. When the IPCD was removed, AES was re-applied until discharge Comparison (n=39): AES, above knee. Duration: started preoperatively, worn until discharge	Age 92.3% >40 years Males and females (31:46) 16.7% malignant condition United States	confirmed by angiography Fatal PE (time-point not reported): method of confirmation not reported	
Chandhoke 1992[50]	Intervention (n=47): IPCD, full length Duration: applied intra-operatively and continued post-op for 5days or until patient became fully ambulant Comparison (n=53): VKA, (warfarin, variable dose). Duration: started on the night of the operation, until discharge	n=100 People having urological surgery (radical prostatectomy 81%, radical cystectomy 9%, other pelvic surgery 3%, kidney surgery 7%) Duration of surgery >2 hours Age (mean, SD): intervention, 67.5 (7.1), comparison, 66.1 (6.4) Male and Female (99:1) Cancer 99% United States	All-cause mortality (1-2 weeks) DVT (5 days): confirmed by venography and ultrasound PE (1-2 weeks): confirmed by venography and ultrasound	
Clarke-Pearson 1983 [54]	Intervention (n=88): UFH (5000U, 2 x daily) Duration: 2 hours before surgery, for 7 days Comparison (n=97): No VTE prophylaxis	n=185 People having gynaecological malignancy surgery Age >20 years Female Cancer 100% United States	DVT (42 days): confirmed by fibrinogen counting, impedance plethysmography and venography PE (42 days): confirmed by ventilation-perfusion scanning and/or pulmonary arteriography Fatal PE (42 days): confirmed at autopsy	

Included studies	Intervention and comparison	Population	Outcomes	Comments
Clarke-Pearson 1984A[55]	Intervention (n=97): IPCD, below knee. Duration: applied at time of anaesthesia, until discharge from recovery room or for 1 day Comparison (n=97): No VTE prophylaxis	n=194 People having major surgery for gynaecologic malignancies Duration of surgery (mean): 233 minutes Female Cancer 100% United states	DVT (42 days): confirmed by I-labelled fibrinogen counting and impedance plethysmography and ascending venography PE (42 days): ventilation perfusion lung scanning, and pulmonary arteriography Fatal PE (42 days): confirmed by autopsy	
Clarke-Pearson 1984B[57]	Intervention (n=55): IPCD, below knee Duration: applied at time of anaesthesia for 5 days Comparison (n=52): No VTE prophylaxis	n=107 People having major surgery for gynaecologic malignancies Duration of surgery >85 minutes Age >20 years Female Cancer 100% United states	All-cause mortality (42 days) DVT (42 days): confirmed by I-fibrinogen counting and impedance plethysmography PE (42 days): ventilation perfusion lung scanning, and pulmonary arteriography	
Clarke-Pearson 1993[56]	Intervention (n=107): UFH (5000U), 3 x daily Duration: started 16 hours before surgery (3 doses given preoperatively), for 7 days, until fully ambulated or until discharge Comparison (n=101): IPCD, below knee. Duration: applied at induction of anaesthesia, for 5 days, until fully ambulant or until discharge	n=208 People having gynaecologic oncology surgery Duration >80 minutes Age >22 years Female Cancer 76.4% United States	DVT (until discharge): confirmed by fibrinogen uptake test, impedance plethysmography, duplex Doppler ultrasound and ascending contrast venography PE (30 days): ventilation perfusion lung scanning and pulmonary arteriography	

Included studies	Intervention and comparison	Population	Outcomes	Comments
Coe 1978[58]	Intervention 1 (n= 28): UFH (5000 U, 2 x daily) Duration: 2 hours before surgery, until discharge Intervention 2 (n=29): Intermittent pneumatic compression device (IPCD), calf length. Duration: applied after induction of anaesthesia until discharge Comparison (n=24): No VTE prophylaxis (control group, no further details reported)	n=81 People undergoing urologic surgery Duration of surgery (mean) 234 minutes Age (mean, SD): intervention 1 = 63 (16) intervention 2 = 55 (11), control = 51 (18) Gender not reported United States	DVT (until discharge): confirmed by I fibrinogen scan technique, phlebography PE (until discharge): confirmed by chest roentgenography, lung scan, or pulmonary angiography	
Fasting 1985[92]	Intervention (n=52): AES, thigh length Duration: applied the evening before surgery and worn for at least five days until mobile Comparison (n=45): UFH, (5000U 2 x daily). Duration: started the evening before surgery for at least 5 days until mobile. All patients received a dose 2-3hrs before surgery	n=97 People having general surgery (gastro-duodenal 14.4%, large intestine 9.3%, rectal 14.4%, biliary 36.1%, urological 19.6%, other 6.2%) Surgery duration >1hr Age (mean, range): intervention, 60 (39-87), comparison, 60 (39-80) Male and female (49:48) Cancer 31.9% Denmark	Major bleeding (time-point not reported): defined as major post-operative haemorrhagic complications Fatal PE (time-point not reported): confirmed by autopsy	
Fricker 1988[102]	Intervention (n=40): LMWH, standard dose (dalteparin, 2500U, 2 x daily). Duration: started 2 hours before surgery and 12 hours after first administration, followed by LWMH, standard dose (dalteparin 5000U, 1 x	n=80 People having surgery of a malignant tumour of the abdomen or pelvis Duration >30 minutes Age >40 years Males and females (8:72)	DVT (10 days): confirmed by I-fibrinogen uptake test and venography PE (up to 8 weeks): confirmed by lung scintigraphy and arterial gazometry	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	daily) for 10 days Comparison (n=40): UFH (5000U, 3 x daily). Duration: started 2 hours before surgery, for 10 days	Cancer 100% France	Major bleeding (4 weeks): defined as severe postoperative bleeding requiring withdrawal of treatment	
Gallus 1973[110]	Intervention (n=108): UFH (5000U, 3 x daily) Duration: started 2 hours before surgery until ambulant Comparison (n=118): No VTE prophylaxis	n=226 People having general surgery (cholecystectomy 37.6%, gastric surgery 16.8%, large bowel surgery 15%, laparotomy 4%, pancreatic surgery 1.3%, abdominal aneurysm 1.3%, hernia repair 5.8%, thoracotomy 4%, laminectomy 6.6%, hip replacement 7.5%)* Cancer = 15.5% Age >40 years Males and Females (92:134) Canada *Data on emergency hip surgery and medical patients has been excluded	DVT (mean 8.5-9.8 days): confirmed by I-fibrinogen scanning and venography	
Gallus 1976[109]	Intervention (n=408): UFH (5000U, 3 x daily) Duration: started 2 hours before surgery, for 7 days or until discharge Comparison (n=412): No VTE prophylaxis	n=820 People having major abdominothoracic surgery (gallbladder 47.9%, stomach 12.8%, large bowel 11%, other intraabdominal 6%, hernia 9.8%, chest 4.8%. spine 9.1%) Duration of surgery (mean, range) 92, 18-310 minutes Age >40 years Cancer 17%	DVT (mean 8.4-9.1 days): confirmed by I-labelled fibrinogen scanning, and phlebography	

Included studies	Intervention and comparison	Population	Outcomes	Comments
		Canada		
Gao 2012[111]	Intervention (n=52): • AES, length undefined circumference • IPCD, thigh length Duration: AES was applied pre-operatively and IPCD was applied intra and postoperatively until ambulant Comparison (n=56): AES, length undefined Duration: applied pre-operatively until ambulant	n=108 People gynaecological pelvic surgery (laparotomy 25%, laparoscopic surgery 55.6%, vaginal surgery 19.4%) Age >60 years Female Cancer 64.8% China	DVT (time-point not reported): confirmed by Doppler ultrasound PE (time-point not reported): confirmed by pulmonary angiography	
Gonzalez 1996[118]	Intervention (n=84): LMWH, standard dose (bemiparin, 2500U, 1 x daily). Duration: started 2 hours before surgery for 7 days Comparison (n=82): UFH (5000U, 2 x daily). Duration: started 2 hours before surgery for 7 days	n=166 People having abdominal surgery (cholecystectomy 52.6%, herniotomy 20.5%, pilorotomy 5.2%, other 21.8%) Duration >30 minutes Age >40 years Males and females (65:101) Spain	All-cause mortality (8 days) DVT (8 days): confirmed by Doppler and plethysmography PE (8 days): confirmed by perfusion/ventilation lung scanning and angiography Major bleeding (8 days): defined as needing a transfusion of 2 or more units of whole blood, haemoglobin less than 2 g/l, central bleeding and reoperation because of bleeding	
Gordon-Smith 1972[120]	Intervention (n=48): UFH (5000U), injected subcutaneously every 12 hours. Duration: started one hour before surgery, for 5 days (a total of 10	n=98 People having general surgery (abdominal 87.8%, prostatectomy 4.1%, nephrectomy/ ureterolithotomy 4.1%,	DVT (time-point not reported): confirmed by I-fibrinogen method PE (time-point not reported):	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	doses) Comparison (n=50): No VTE prophylaxis	radical mastectomy 4.1%) Age >40 years Male and female (49:49) Cancer 32.7% UK	confirmed by phlebography	
Hartl 1990[136]	Intervention (n=126): LMWH, low dose (dalteparin, 2500U, 1 x daily) Duration: started 2 hours before operations for at least 7 days post op and fully ambulant Comparison (n=124): UFH (5000U, 2 x daily) Duration: started 2 hours before operations for at least 7 days post op and fully ambulant	n=250 People having abdominal surgery Duration of surgery (mean): intervention 91.7, comparison 106.4 minutes Aged >40 years Males and females (144:106) Cancer 29.6% Austria	All-cause mortality (time-point not reported): confirmed by autopsy DVT (time-point not reported): confirmed by fibrinogen uptake test and venography Major bleeding (time-point not reported): defined as bleeding requiring transfusion >2 units of blood Fatal PE (time-point not reported): confirmed by autopsy	
Hata 2016[137]	Intervention (n=152): • UFH (5000U) • Fondaparinux (2.5mg, 1 x daily) • Mechanical thromboprophylaxis (AES + IPCD) UFH started 6 hours after wound closure and continued every 12 hours until the day after surgery. Fondaparinux started on postoperative day 2 until day 5. Mechanical thromboprophylaxis used until full ambulatory	n=298 People with urological malignancy Duration of surgery >45 minutes Age >40 years Males and females 282:16 Japan	PE (time-point not reported): method of confirmation not reported Major bleeding (time-point not reported): defined as fatal bleeding, bleeding at vital organs, bleeding or hematoma around the surgical beds necessitating reoperation, or bleeding necessitating transfusion of >400mL red blood	If eGFR ranged from 30-50 mL/min/1.73^2 and the risk of bleeding was high, prophylaxis could be reduced to 1.5mg (fondaparinux) or 2000U daily (enoxaparin), at the discretion of the physician

Included studies	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=146): • UFH (5000U) • LMWH, standard dose (enoxaparin, 2000U, 2 x daily) • Mechanical thromboprophylaxis (AES + IPCD) UFH started 6 hours after wound closure and continued every 12 hours until the day after surgery. LMWH started on postoperative day 2 until day 5. Mechanical thromboprophylaxis used until full ambulatory		cells prepared form whole blood, or >2g/dL decrease in haemoglobin level within 48 hours after bleeding onset	
Hauch 1988[138]	Intervention (n=20): LMWH, standard dose (tinzaparin, 3500U, 1 x daily). Duration: started 2 hours before operation, until postoperative day 7 or discharge Comparison (n=22): LMWH, low dose, (tinzaparin, 2500U, 1 x daily). Duration: started 2 hours before operation, until postoperative day 7 or discharge	n=42 People having major abdominal surgery (biliary tract surgery 17.1%, gastric surgery 14.3%, colorectal surgery 48.6%, other 20%) Duration of surgery >1 hour Age >40 years Male and female (13:22) Denmark	DVT (7 days): confirmed by venography PE, symptomatic (1 month): method of confirmation not reported Major bleeding (1 month): defined as major bleeding complications Fatal PE (1 month): confirmed by autopsy	
Holford 1976[143]	Intervention (n=48): AES, above knee Duration: applied 12 hours before operation until fully ambulant (4 or 5 days post op) Comparison (47): No VTE prophylaxis (control group, no further details reported)	n=95 People having major surgery (abdominal, pelvic, abdominal and pelvic or thoracic 9.5%) Age >40 years Cancer 20.4% UK	All-cause mortality (time-point not reported) DVT (time-point not reported): confirmed by I-fibrinogen test PE (time-point not reported): confirmed by lung	

Included studies	Intervention and comparison	Population	Outcomes	Comments
			scanning	
Kaaja 1992[156]	Intervention (n=37): LMWH, low dose (enoxaparin, 20mg, 1 x daily). Duration: started 2 hours before surgery for 3 days Comparison (n=31): UFH, 5000U, 2 x daily). Duration: started 2 hours before surgery for 3 days	n=68 People having abdominal hysterectomy Age >35 years Female Cancer 25% Finland	PE (3-4 weeks): confirmed by lung scanning Major bleeding (time-point not reported): defined as bleeding necessitating reoperation and/or blood transfusion, and cessation of heparin administration	
Kakkar 1972[160]	Intervention (n=39): UFH (5000U, 2 x daily) Duration: started 2 hours before surgery for 7 days Comparison (n=39): No VTE prophylaxis	n=78 People having major surgery (gastric 24.4%, colonic 16.7%, biliary, 33.3% thoracic 5.1%, urological 16.7%, laparotomy 3.8%) Age >40 years Male and female (45:33) United States	DVT (10 days): confirmed by I-labelled fibrinogen test PE (time-point not reported): method of confirmation not reported	
Kakkar 1993[159]	Intervention (n=1894): LMWH, low dose (dalteparin, 2500U, 1 x daily) Duration: started 1-4 hours before operation, for at least 5 days and until fully mobile Comparison (n=1915): UFH (5000U), 2 x daily Duration: started 1-4 hours before operation, for at least 5 days and until fully mobile	n=3809 People having major abdominal surgery (colectomy 23.4%, abdominoperineal resection 4.5%, cholecystectomy 25%, other biliary procedures 1.3%, laparotomy 3.9%, gynaecological procedure 25.4%, oesophageal procedure 2.8%, gastric procedure 6.6%, urological procedure 2.7%, other 3.6%) Duration >30 minutes Age > 40 years Male and female (1314:2495)	All-cause mortality (4-8 weeks) PE (4-8 weeks): confirmed by ventilation/perfusion scanning or pulmonary angiography Major bleeding (4-8 weeks) defined as: blood loss during the perioperative period that required discontinuation of prophylaxis, when bleeding was clearly attributable to the trial drug, when bleeding	

Included studies	Intervention and comparison	Population	Outcomes	Comments
		Cancer 36.9% UK	required reoperation to control it, or when a wound haematoma developed whether or not it required evacuation. Fatal PE (4-8 weeks): confirmed by autopsy	
Kakkar 2010[158]	Intervention (n=315): extended duration LMWH, high dose (bemiparin, 3500U, 1 x daily) Duration: before randomisation, all patients received LMWH for 8±2 days, starting 6 hours after surgery. Patients then received LMWH for 20 ±2 additional days Comparison (n=310): standard duration LMWH, high dose (bemiparin, 3500U) + placebo (0.9% sodium chloride 0.2mL). Duration: before randomisation, all patients received LMWH for 8±2 days, starting 6 hours after surgery. Patients then received placebo for 20±2 additional days	n=625 People having abdominal or pelvic surgery for cancer (gastrointestinal tract (colorectal, gastric and other) 80.6%, urologic 7.5%, female reproductive organs 11.4%, retroperitoneal 0.5%) Duration >30 minutes Age >40 years Males and females (330:295) 34 centres in 3 countries (UK, Spain, Italy)	All-cause mortality (90 days) DVT (28 days): confirmed by venography or Doppler ultrasound PE (28 days): confirmed by perfusion/ventilation lung scintigraphy, pulmonary arteriography or spiral computed tomography Major bleeding (22 days): defined as fatal bleeding, clinically overt bleeding, bleeding leading to a transfusion of 2 or more units of packed cells or whole blood, retroperitoneal or intracranial bleeding, or clinically overt bleeding warranting treatment cessation	
Koller 1986A[170]	Intervention (n=23): LMWH, high dose (dalteparin, 7500U, 1 x daily) Duration: started one hour before operation,	n=43 People having general surgery (herniotomy 51.2%, cholecystectomy 18.6% , breast operation	All-cause mortality (time-point not reported) DVT (30 days): confirmed by	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	for a minimum of 5 days Comparison (n=20): UFH (5000U), 2 x daily Duration: started one hour before operation, for a minimum of 5 days	9.3%, vagotomy 4.7%, colon resection 9.3%, lung resection 2.3%, other 4.7%) Age >20 years Males and females (28:15) Switzerland	fibrinogen uptake test and venography Major bleeding (time-point not reported): defined as bleeding requiring discontinuation of prophylaxis	
Koller 1986B[170]	Intervention (n=74): LMWH, low dose (dalteparin, 2500U, 1 x daily) Duration: started one hour before operation, for at least 5 days Comparison (n=72): UFH (5000U), 2 x daily Duration: started one hour before operation, for at least 5 days	n=146 People having general surgery (herniotomy 60.3%, cholecystectomy 17.8%, prox. selective vagotomy 2.1%, colon resection 5.5%, breast operation 9.6%, other 4.5%) Age >20 and <80 Males and females (89:57) Cancer 14.4% Switzerland	All-cause mortality (time-point not reported) DVT (30 days): confirmed by fibrinogen uptake test and venography PE (30 days): confirmed by pulmonary perfusion/ventilation scans Major bleeding (time-point not reported): defined as bleeding complications leading to discontinuation of prophylaxis, and transfusion >2 units of blood	
Lahnborg 1975[175,176]	Intervention (n=58): UFH (5000U, 2 x daily) Duration: started 2-5 hours before surgery, for 5 days Comparison (n=54): No VTE prophylaxis	n=112 People having major abdominal surgery Age >40 years Sweden No further details reported	All-cause mortality (5 days) PE (time-point not reported): confirmed by pulmonary photo scanning Major bleeding (time-point not reported): not defined	
Liezorovicz 1991[193]	Intervention 1 (n=431): LMWH, low dose (tinzaparin, 2500U, 1 x	n=1290	All-cause mortality (1 month)	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	daily) Duration: started 2 hours before operation, for at least 7 days and maximum of 10 days Intervention 2 (n=430): LMWH, standard dose (tinzaparin, 3500U, 1 x daily) Duration: started 2 hours before operation, for at least 7 days and maximum of 10 days Comparison (n=429): UFH (5000U), 2 x daily Duration: started 2 hours before operation, for at least 7 days and maximum of 10 days	People having general surgery (abdominal 71.4%, gynaecological 13.5%, urological 9.8% or thoracic 5.3%) Duration > 30minutes Age >40 years Male and female (513:777) Cancer 38.5% France and UK	DVT (8 days): confirmed by fibrinogen uptake test and venography PE (1 month): confirmed by angiography Major bleeding (discharge – 1 month): defined as haemorrhage needing transfusion and/or reintervention and/or treatment discontinuation	
Marassi 1993 [202]	Intervention (n=31): LMWH, high dose (nadroparin, 3825U, 1 x daily). Duration: started 2 hours before operation, for 7 days Comparison (n=33): No VTE prophylaxis	n=64 People having cancer-related abdominal surgery Age > 40 years Males and females (36:25) Cancer surgery 100% Italy	DVT (7 days): confirmed by FUT and venography	
Maxwell 2001[204]	Intervention (n=106): IPCD, length not reported. Duration: applied at induction of anaesthesia and continued for first 5 days postoperatively. Device stopped when patient was walking and restarted when back in bed. Comparison (n=105): LMWH, standard dose, (dalteparin, 5000U, 1 x	n=228 People having gynaecological surgery (duration, median: intervention 199 minutes, comparison 197 minutes) Age >40 years Females Cancer 74.9% United states	DVT (30 days): confirmed by real-time US compression technique with duplex and colour Doppler imaging PE (30 days): method of confirmation not reported Thrombocytopaenia (time-point not reported)	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	daily). Duration: 2500U given 1-2 hours before surgery and 12 hours after first dose. Then from postoperative day 1, 5000U was administered once daily up to post-operative day 5. If the patient was confined to bed after day 5, continued prophylaxis until day of discharge or ambulatory.			
McLeod 2001[210]	Intervention (n=674): LMWH, standard dose, (enoxaparin, 40mg, 1 x daily). Duration: started 2 hours before surgery, for 10 days Comparison (n=675): UFH, (5000 units, 3 x daily) Duration: started 2 hours before surgery, for 10 days	n=1349 People having abdominal (colorectal) surgery Duration >1 hour Age (mean, SD): intervention 52 (18), control 50 (17) Male and female (731:618) Cancer 35% Canada	PE (10 days): confirmed by lung scan or pulmonary angiogram Major bleeding (10 days): defined as intracranial, retroperitoneal, or clinically overt haemorrhage associated with a decrease in the haemoglobin level of more than 20 g/L, the transfusion of 2 or more units of packed cells, or the need for surgical intervention	
Nagata 2015[223]	Intervention (n=16): • Foot impulse device (FID) • IPCD, below knee • LMWH, standard dose (enoxaparin, 20mg, 2x daily) Duration: FID was applied immediately before surgery. Post operatively, patients switched to IPCD until after the first LMWH injection on	n=30 People having major abdominal or pelvic surgery (hysterectomy 53.3%, laparotomy 30%, debulking surgery 10%, tumour sampling 6.7%) Duration >45 minutes Age >40 years Females 100% cancer	DVT (11 days): confirmed by contrast CT PE (11 days):confirmed by contrast CT Major bleeding (11 days): defined as red blood cell transfusion of more than two units, a decrease in haemoglobin	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	postoperative day 2. LMWH commenced on postoperative day 2 for 7 days Comparison (n=14): • FID • IPCD, below knee Duration: FID was applied immediately prior to surgery. Post operatively, patients switched to IPCD until fully ambulated	Japan	concentration of more than 2g/dL, intracranial, intraocular, gastrointestinal, epidural haemorrhage or bleeding from the wounds, the abdomen or retroperitoneal cavity that required surgical treatment Thrombosytopenia (6 days)	
Nicolaides 1983[232]	Intervention 1 (n=50): • IPCD, full leg • AES, length not reported Duration: IPCD worn during surgery and for 72 hours post-op or until ambulant, then AES applied until discharge Intervention 2 (n=50): UFH, (5000U, 2 x daily) Duration: started 2 hours before operation, until discharge Comparison (n=50): Electrical calf stimulation at 12 impulses/min. Duration: started after induction of anaesthesia and continued for duration of operation	n=150 People having abdominal surgery Age >30 years Gender not reported Cancer 37.3% UK	DVT (until discharge): confirmed by 125I FUT	
Nurmoha med 1995[235]	Intervention (n=718): LMWH, low dose (enoxaparin, 20mg 1 x daily) Duration: started 2 hours before operation, for 10 days or until discharge Comparison (n=709):	n=1427 People having general surgery (gastric 12.5%, cholecystectomy 23%, other biliary 2.4%, colon/rectum 28.9%, herniotomy 6%, hysterectomy 9.8%, other gynaecological 3.8%,	All-cause mortality (time point not reported) DVT (10 days): confirmed by fibrinogen 1 125 uptake test and unilateral venography	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	UFH (5000U), 3 x daily Duration: started 2 hours before operation, for 10 days or until discharge	urological 8%, other 4.2%) Duration of surgery >45 minutes Aged >40 years Males and females (670:734) Cancer 35.8% 20 centres in Belgium, Germany, The Netherlands, Spain, UK, and New Zealand	PE (time point not reported): clinical suspicion or autopsy Major bleeding (time point not reported): defined as clinically overt with either a fall of haemoglobin of 20g/L or when it led to a transfusion of 2 or more units of packed cells, or if it was retroperitoneal or intracranial Fatal PE (time-point not reported): confirmed by autopsy	
Ockelford 1989 [236]	Intervention (n=102): LMWH low dose, (dalteparin, 2500U, 1 x daily). Duration: started 1-2 hours before operation, for 5-9 days Comparison (n=95): No VTE prophylaxis (placebo)	n=197 People having abdominal surgery Duration >30 minutes Age >40 years Males and females Cancer surgery 43% New Zealand	All-cause mortality (42 days) DVT (42 days): confirmed by FUT PE (42 days): not reported Major bleeding (42 days): defined as when treatment discontinued because of excess bleeding Thrombocytopaenia (42 days): not reported	
Onarheim 1986[238]	Intervention (n=25): LMWH, standard dose (dalteparin, 5000U, 1 x daily). Duration: started 2 hours before surgery, for 6 days Comparison (n=27): UFH 5000U, 2 x daily	n=52 People having major abdominal surgery for gastric, colonic, or rectal malignancy Age >40 years Cancer 100%	All-cause mortality (30 days) DVT (30 days): confirmed by fibrinogen uptake test and phlebography PE (30 days):	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	Duration: started 2 hours before surgery, for 6 days	Norway	method of confirmation not reported Major bleeding (30 days): defined as bleeding requiring reoperation or interruption of prophylaxis	
Osman 2007[239]	Intervention 1 (n=25): LMWH, standard dose, (tinzaparin, 3500U, 1 x daily) Duration: for 1 week post operatively. No further details reported Intervention 2 (n=25): UFH, (5000U), 2 x daily Duration: for 1 week post operatively. No further details reported Comparison (n=25): No VTE prophylaxis	n=75 People having live-donor renal transplantation Duration not reported Age >16 years Male and female (52:23) Egypt	DVT (2 weeks): radiologically, ultrasonography, CT or MRI and isotope renography were used to diagnose postoperative complications PE (2 weeks): radiologically, ultrasonography, CT or MRI and isotope renography were used to diagnose postoperative complications Major bleeding (2 weeks): defined as massive haemorrhage necessitating exploration	
Porteous 1989[245]	Intervention (n=56): AES, above knee. Duration: worn until discharge. No further details reported Comparison (n=58): AES, below knee. Duration: worn until discharge. No further details reported	n=124 People having major abdominal surgery Duration of surgery (mean, SD): intervention 110 (39), comparison 115 (44) Age >40 years Males and females (49:65) Malignant disease 40.4% UK	DVT (time-point not reported): confirmed by I-labelled fibrinogen uptake test and phlebography	
Rasmussen	Intervention (n=205):	n=427	All-cause mortality	

Included studies	Intervention and comparison	Population	Outcomes	Comments
2006[251]	• LMWH, standard dose, extended duration (dalteparin, 5000 U, 1 x daily). • AES, length not reported Duration: LMWH started the day before surgery, for 28 days. AES worn for 7 days <u>Comparison (n=222):</u> • LMWH, standard dose, standard duration (dalteparin, 5000 U, 1 x daily) • AES length not reported Duration: LMWH started the day before surgery, for 7 days. AES worn for 7 days	People having major abdominal surgery Duration > 1 hour Age >18 years Male and female (174:169) Denmark and Norway	(2 months) DVT (day 28): confirmed by bilateral venography PE (2 months): confirmed by ventilation/perfusion scanning Major bleeding (28 days): defined as bleeding that resulted in death, fall in haemoglobin ≥ 2g/dl, transfusion ≥2 units of blood, retroperitoneal, intracranial, intraocular, resulted in life threatening event, or surgical/medical intervention required to stop it Fatal pulmonary embolism (up to 2 months): method of confirmation not reported	
Rasmussen 1988[250]	<u>Intervention 1 (n=74):</u> AES, knee length Duration: applied the evening before surgery, for at least 5 days <u>Intervention 2 (n=85):</u> UFH (5000U), administered subcutaneously every 12 hours. Duration: started the evening before surgery, for at least 5 days <u>Comparison (n=89):</u> • AES, knee length	n=248 People having major abdominal surgery (colon+rectum 21%, biliary 30.6%, gastric+pancreas 12%, urologic 14.9%, gynaecologic 14.1%, other 7.3%) Duration >1 hour Age >40 years Males and females (109:139) Denmark	All-cause mortality (time-point not reported) PE (time-point not reported): method of confirmation not reported Major bleeding (time-point not reported): defined as major postoperative haemorrhage	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	• UFH (5000U) Duration: as above			
Sakon 2010[260]	Intervention (n=113): • IPCD, length not reported • LMWH, standard dose (enoxaparin 20mg 2 x daily) Duration: all patients received at least one course of postsurgical IPCD before first LMWH dose. No further details on IPCD. LMWH started 24-36 hours after surgery and continued for 14 days (and for at least 7 consecutive days). Comparison (n=38): IPCD length not reported Duration: left to the discretion of the investigator	n=151 People having a laparotomy for cancer (stomach 42.1%, rectum 14.9%, colon 21.9%, prostate 4.4%, uterus 4.4%, ovary 2.6%, hepatic 2.6%, other 13.2%) * Duration >45 minutes Age >40 years Males and females (69:45) 100% cancer Japan *total is more than 100% as some patients had surgery at multiple sites	DVT (14 days): confirmed by ultrasonography and venography PE (14 days): confirmed by ventilation/perfusion lung scan, pulmonary angiography or computerised tomography Major bleeding (14 days): defined as the event resulted in death, was clinically overt, was retroperitoneal, intracranial, or intraocular, or resulted in serious or life threatening clinical events, or required surgical or medical intervention to control the event	
Scurr 1981[268]	Intervention (n=33): foot pump. Duration: applied from the beginning of the procedure until the patient regained consciousness Comparison (n=33): No VTE prophylaxis	n=66 People having major abdominal surgery Duration >20 minutes Age >40 years Cancer 77% UK	All-cause mortality (7 days) DVT (7 days): confirmed by fibrinogen scanning	
Soderdahl 1997[272]	Intervention (n=47): IPCD, thigh-length. Comparison (n=43): IPCD, calf-length Duration: begun pre-anaesthetic and continued until patient fully ambulatory or	n=90 People having abdominal (urological) surgery (duration not reported) Age (mean, range): intervention 64.8 (46-90), comparison 58.6 (24-77)	DVT (3 months): confirmed by bilateral duplex ultrasound PE (3 months): confirmed by ventilation perfusion scan and pulmonary	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	until discharge	Male and female United States	angiography Fatal PE (3 months): method of confirmation not reported	
Song 2014[273]	Intervention (n=108): • LMWH, standard dose (enoxaparin 40mg, 1 x daily) • IPCD, length not reported Duration: LMWH started post-operatively until discharge, IPCD applied pre-operatively until discharge Comparison (n=112): IPCD, length not reported Duration: applied pre-operatively until discharge	n=220 People with cancer having gastrectomy (100% adenocarcinoma) Age >20 years Male to female (150:70) Cancer 100% South Korea	DVT (4 days): confirmed by duplex ultrasonography PE (30 days): 'detected' Major bleeding (30 days): definition not reported	
Strand 1975[284]	Intervention (n=50): UFH (5000U, 2 x daily) Duration: started 1-3 hours before surgery or on admission, for 7 days Comparison (n=50): No VTE prophylaxis (placebo)	n=100 People having gastrointestinal or urinary tract surgery (stomach 16.7%, small intestine 2.9%, biliary 21.6%, colon 21.6%, rectum 4.9%, urinary 27.4%, other 6.9%) Age >30 years Males and females (49:51) Cancer 28% Denmark	DVT (10 weeks): confirmed by I fibrinogen method PE (10 weeks): method of confirmation not reported Fatal PE (10 weeks): confirmed by autopsy	
Taberner 1978[286]	Intervention 1 (n=49): UFH (5000U, 2 x daily) Duration: started 2 hours before surgery on, for 7 days Intervention 2 (n=48): VKA (acenocoumarol), 6mg	n=145 People having abdominal or vaginal surgery (hysterectomy or laparotomy 58.6%, pelvic floor repair 41.4.2%) Age >40 years	DVT (7 days): confirmed by fibrinogen scan	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	Duration: started at least 5 days before surgery Comparison (n=48): No VTE prophylaxis (placebo)	Cancer 5.5% UK		
Torngren 1978[290,291]	Intervention (n=63): UFH (5000U, 2 x daily) Duration: started 2 hours before surgery or on admission, for 6-8 days Comparison (n=61): No VTE prophylaxis	n=124 People having abdominal surgery Duration of surgery >20 minutes Age >40 years Males and females (66:58) Cancer 24% Sweden	All-cause mortality (6-8 days): confirmed by autopsy DVT (up to 14 days): confirmed by I-fibrinogen test PE (6-8 days): confirmed by autopsy Major bleeding (6-8 days): defined at bleeding requiring a transfusion Fatal PE (6-8 days): confirmed by autopsy	
Tsapogas 1971 [292]	Intervention (n=51): AES, below knee. Duration: day of surgery until discharge Comparison (n=44): No VTE prophylaxis	n=95 People having major abdominal surgery Age >40 years Male and female (93:2) USA	DVT (7 days): confirmed by fibrinogen uptake test and phlebography	
Turner 1984 [293]	Intervention (n=104): AES, above knee Duration: started on day of admission, discontinuation point not reported Comparison (n=92): No VTE prophylaxis	n=196 People having elective gynaecological surgery Age >35 years Female UK	DVT (time-point not reported): confirmed by Fibrinogen Uptake Test PE (time-point not reported): method of confirmation not reported	
Turpie	Intervention (n=650):	n=1309	All-cause mortality	The use of AES was left to the

Included studies	Intervention and comparison	Population	Outcomes	Comments
2007[294]	• Fondaparinux (2.5mg, 1 x daily) • IPCD, mixed length Duration: started 6-8 hours after surgery, provided that haemostasis was achieved, or 2 hours after removal of intrathecal or epidural catheter. Second injection given 16-28 h after 1st injection. Duration was 5-9 days. IPCD duration was left to the investigators discretion <u>Comparison (n=659):</u> IPCD, mixed length Duration: left to the investigators discretion	People having abdominal surgery Duration >45 minutes Age > 40 years Male and female (635:650) United States	(32 days) DVT (days 5-10): confirmed by bilateral ascending contrast venography PE, symptomatic (32 days): confirmed by a high-probability lung scan, non-high probability lung scan defect plus confirmed DVT, pulmonary angiography, helical computed tomography, or autopsy) Major bleeding (day 32): defined as bleeding that was fatal, retroperitoneal, intracranial, or involved any other critical organ, led to intervention, or was associated with a bleeding index of 2.0 or more. Fatal PE (32 days): confirmed by: autopsy	investigator's discretion
Van Vroonhoven 1974[302]	<u>Intervention (n=50):</u> UFH (dose not reported, 2x daily). Duration: begun 2 hours before operation, for 8 days <u>Comparison (n=50):</u> VKA (acenocoumarol, PTT 5-10% of normal). Duration: Begun on evening of day of op, or 1st post-op day. Continued for 7 days	n=100 People having general surgery (gastric 24%, biliary 28%, colonic 15%, herniotomy 16%, abdominal wall 6%, laparotomy 6%, other 5%) Age >40 years Cancer 18% Netherlands	DVT (time-point not reported): confirmed by I-fibrinogen test Major bleeding (time-point not reported): defined as overt bleeding complications	

Included studies	Intervention and comparison	Population	Outcomes	Comments
Vandendris 1980 [303]	Intervention (n=31): UFH (5000U, 3 x daily) Duration: started 2 hours before operation for 6 days Comparison (n=33): No VTE prophylaxis (placebo, 0.2 ml distilled water)	n=64 People having urologic surgery Age (mean): intervention 72.2, comparison 70 Belgium	DVT (time-point not reported): confirmed by I-labelled fibrinogen test and clinical examination PE (time-point not reported): confirmed by clinical examination	Patients with varicose veins wore AES during and after the operation
Wille-Jorgensen 1985 [317]	Intervention (n=94): • AES, thigh length • UFH (5000U 2 x daily) Duration: AES applied before surgery during the observation period. UFH administered 1 hour preoperatively for 7 days or until discharge Comparison (n=102): UFH (5000U, 2 x daily). Duration: administered 1 hour preoperatively for 7 days or until discharge	n=196 People having abdominal surgery Duration >45 minutes Age >39 years Male and female (105:71) Denmark	DVT (7 days): confirmed by Fibrinogen Uptake Test, and phlebography and perfusion lung scan if Fibrinogen Uptake Test was positive PE (30 days): confirmed by scintigraphy or autopsy Fatal PE (30 days): confirmed by scintigraphy	
Wille-Jorgensen 1991 [316]	Intervention (n=94): • AES, above knee • UFH (5000U 2 x daily) Duration: AES applied preoperatively and worn until full mobilisation. UFH administered on day of surgery for 7 days or until discharge. Comparison (n=84): UFH (5000U 2 x daily) Duration: administered on day of surgery for 7	n=178 People having abdominal surgery Duration >1 hour Age >39 years Male and female (58:102) Denmark	All-cause mortality (30 days) DVT (30 days): confirmed by I-fibrinogen uptake test and phlebography PE (30 days): confirmed by perfusion pulmonary scintigram and roentgenogram	

Included studies	Intervention and comparison	Population	Outcomes	Comments
	days or until discharge			

Table 169: Clinical evidence summary: AES (above knee) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (above knee) versus no VTE prophylaxis (95% CI)
All-cause mortality	291 (2 studies) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 16 fewer to 16 more)[d]
DVT	291 (2 studies) time-point not reported	MODERATE[a] due to risk of bias	RR 0.41 (0.23 to 0.73)	194 per 1000	115 fewer per 1000 (from 52 fewer to 150 fewer)
PE	291 (2 studies) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0 to 6.68)	7 per 1000	6 fewer per 1000 (from 7 fewer to 39 more)

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

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

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

d Risk difference calculated in Review Manager

Table 170: Clinical evidence summary: AES (below knee) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (below knee) versus no VTE prophylaxis (95% CI)
DVT	95 (1 study) 7 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.29 (0.06 to 1.35)	136 per 1000	97 fewer per 1000 (from 128 fewer to 48 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (below knee) versus no VTE prophylaxis (95% CI)

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

Table 171: Clinical evidence summary: AES (undefined) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (undefined) versus no VTE prophylaxis (95% CI)
DVT	200 (1 study) 7 days	MODERATE[a] due to risk of bias	RR 0.43 (0.25 to 0.73)	359 per 1000	205 fewer per 1000 (from 97 fewer to 269 fewer)

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

Table 172: Clinical evidence summary: AES (above knee) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (above knee) versus UFH (95% CI)
Fatal PE	97 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.12 (0 to 5.9)	22 per 1000	20 fewer per 1000 (from 22 fewer to 96 more)

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

Table 173: Clinical evidence summary: AES (below knee) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (below knee) versus UFH (95% CI)
All-cause mortality	159 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 24 fewer to 24 more)[e]
PE	159 (1 study) time-point not reported	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 24 fewer to 24 more)[e]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

Table 174: Clinical evidence summary: AES (above knee) versus AES (below knee)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES above knee versus AES below knee (95% CI)
DVT	114 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	RR 3.11 (0.33 to 28.99)	17 per 1000	36 more per 1000 (from 12 fewer to 483 more)

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

Table 175: Clinical evidence summary: AES (below knee) + UFH versus AES (below knee)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with AES + UFH (95% CI)
All-cause mortality	163 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 24 fewer to 24 more)[e]
PE	163 (1 study) time-point not reported	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 24 fewer to 24 more)[e]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

Table 176: Clinical evidence summary: AES (above knee) + UFH versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (above knee) + UFH versus UFH (95% CI)
All-cause mortality	160 (1 study) up to 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.49 (0.74 to 3.01)	136 per 1000	67 more per 1000 (from 35 fewer to 273 more)
DVT	336 (2 studies) up to 30 days	MODERATE[a] due to risk of bias	RR 0.16 (0.05 to 0.54)	111 per 1000	93 fewer per 1000 (from 51 fewer to 106 fewer)
PE	336		RR 0.35	34 per 1000	23 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (above knee) + UFH versus UFH (95% CI)
	(2 studies) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	(0.07 to 1.68)		(from 33 fewer to 24 more)
Fatal PE	176 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0 to 7.14)	11 per 1000	10 fewer per 1000 (from 11 fewer to 63 more)

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

Table 177: Clinical evidence summary: AES (below knee) + UFH versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (below knee) + UFH versus UFH (95% CI)
All-cause mortality	174 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 22 fewer to 22 more)[e]
PE	174 (1 study) time-point not reported	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 22 fewer to 22 more)[e]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Could not be calculated as there were no events in the intervention or comparison group

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (below knee) + UFH versus UFH (95% CI)
e Risk difference calculated in Review Manager					

Table 178: Clinical evidence summary: AES (above knee) + IPCD (full leg) versus AES (above knee)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (above knee) + IPCD versus AES (95% CI)
DVT	77 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.21 (0.03 to 1.68)	128 per 1000	101 fewer per 1000 (from 124 fewer to 87 more)
PE	77 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.03 (0.07 to 15.82)	26 per 1000	1 more per 1000 (from 24 fewer to 380 more)
Fatal PE	77 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0 to 7)	26 per 1000	22 fewer per 1000 (from 26 fewer to 130 more)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 179: Clinical evidence summary: AES (undefined) + IPCD (full leg) versus AES (undefined)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (undefined) + IPCD versus AES (95% CI)
DVT	108		RR 0.38	250 per 1000	155 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES (undefined) + IPCD versus AES (95% CI)
	(1 study) time-point not reported	LOW[a,b] due to risk of bias, imprecision	(0.15 to 0.99)		(from 2 fewer to 213 fewer)
PE	108 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.08 (0.07 to 16.78)	18 per 1000	1 more per 1000 (from 17 fewer to 282 more)

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

Table 180: Clinical evidence summary: AES (undefined) + IPCD (full leg) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES + IPCD versus UFH (95% CI)
DVT	100 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.43 (0.12 to 1.56)	140 per 1000	80 fewer per 1000 (from 123 fewer to 78 more)

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

Table 181: Clinical evidence summary: AES (undefined) + IPCD (full leg) versus electrical stimulation

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES + IPCD versus electrical stimulation (95% CI)
DVT	100		RR 0.25	240 per 1000	180 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with AES + IPCD versus electrical stimulation (95% CI)
	(1 study) time-point not reported	LOW[a,b] due to risk of bias, imprecision	(0.08 to 0.83)		(from 41 fewer to 221 fewer)

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

Table 182: Clinical evidence summary: Electrical stimulation versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Electrical stimulation versus UFH (95% CI)
DVT	100 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.71 (0.74 to 3.99)	140 per 1000	99 more per 1000 (from 36 fewer to 419 more)

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

Table 183: Clinical evidence summary: Foot pump versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Foot pump versus no prophylaxis (95% CI)
All-cause mortality	66 (1 study) 7 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.82)	30 per 1000	26 fewer per 1000 (from 30 fewer to 145 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Foot pump versus no prophylaxis (95% CI)
DVT	66 (1 study) 7 days	LOW[a,b] due to risk of bias, imprecision	RR 0.4 (0.18 to 0.9)	455 per 1000	273 fewer per 1000 (from 45 fewer to 373 fewer)

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

Table 184: Clinical evidence summary: FID + IPCD (below knee) + LMWH (low dose) versus FID + IPCD (below knee)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with FID + IPCD + LMWH versus FID + IPCD (95% CI)
DVT	30 (1 study) 11 days	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	RR 0.29 (0.03 to 2.5)	214 per 1000	152 fewer per 1000 (from 208 fewer to 321 more)
PE	30 (1 study) 11 days	LOW[a,b] due to risk of bias, imprecision	Peto OR 0.11 (0.01 to 1.13)	214 per 1000	185 fewer per 1000 (from 212 fewer to 21 more)
Thrombocytopaenia	30 (1 study) 6 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 121 fewer to 121 more)[e]

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with FID + IPCD + LMWH versus FID + IPCD (95% CI)
d Could not be calculated as there were no events in the intervention or comparison group e Risk difference calculated in Review Manager					

Table 185: Clinical evidence summary: IPCD (below knee) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IPCD versus no prophylaxis (95% CI)
All-cause mortality	107 (1 study) 42 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 36 fewer to 36 more)[e]
DVT	473 (4 studies) up to 90 days	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.64 (0.26 to 1.59)	165 per 1000	59 fewer per 1000 (from 122 fewer to 97 more)
PE	354 (3 studies) 42 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 2.19 (0.58 to 8.24)	17 per 1000	21 more per 1000 (from 7 fewer to 126 more)
Fatal PE	313 (2 studies) up to 90 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.5 (0.05 to 4.81)	13 per 1000	6 fewer per 1000 (from 12 fewer to 47 more)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs c Downgraded by 1 increment because heterogeneity, 1^2=67%, p=0.03, unexplained by subgroup analysis. d Could not be calculated as there were no events in the intervention or comparison group e Risk difference calculated in Review Manager					

Table 186: Clinical evidence summary: IPCD (full leg) versus IPCD (below knee)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IPCD full length versus IPCD below knee (95% CI)
DVT	90 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.12 (0 to 6.24)	23 per 1000	20 fewer per 1000 (from 23 fewer to 106 more)
PE	90 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 6.79 (0.13 to 343.33)	0 per 1000	Not estimable[c]
Fatal PE	90 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.12 (0 to 6.24)	23 per 1000	20 fewer per 1000 (from 23 fewer to 106 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Could not be calculated as there were no events in the comparison group

Table 187: Clinical evidence summary: IPCD (full leg) versus VKA

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IPCD versus warfarin (95% CI)
All-cause mortality	100 (1 study) 7-14 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 38 fewer to 38 more)[e]
DVT	100 (1 study) 7-14 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 8.58 (0.53 to 139.81)	0 per 1000	Not estimable[F]
PE	100 (1 study)	VERY LOW[a,b,c] due to risk of bias, imprecision,	Peto OR 8.4 (0.17 to 426.1)	0 per 1000	Not estimable[F]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IPCD versus warfarin (95% CI)
	7-14 days	indirectness			

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager
f Could not be calculated as there were no events in the comparison group

Table 188: Clinical evidence summary: ICPD (undefined) + LMWH (standard prophylactic dose) versus IPCD (undefined)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IPCD + LMWH standard dose versus IPCD (95% CI)
DVT	334 (2 studies) 14-30 days	LOW[a] due to risk of bias	RR 0.07 (0.02 to 0.26)	63 per 1000	59 fewer per 1000 (from 47 fewer to 62 fewer)
PE	334 (2 studies) 14-30 days	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 12 fewer to 12 more)[e]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

Table 189: Clinical evidence summary: UFH versus no prophylaxis/mechanical

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with UFH versus no prophylaxis (95% CI)
All-cause mortality	393 (4 studies) 5-8 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.36 (0.1 to 1.27)	46 per 1000	29 fewer per 1000 (from 41 fewer to 12 more)
DVT	1991 (12 studies) 7-70 days	MODERATE[a] due to risk of bias	RR 0.40 (0.30 to 0.53)	138 per 1000	83 fewer per 1000 (from 65 fewer to 97 fewer)
PE	897 (10 studies) 7-70 days	LOW[a,b] due to risk of bias, imprecision	RR 0.60 (0.36 to 1.02)	62 per 1000	25 fewer per 1000 (from 40 fewer to 1 more)
Major bleeding	725 (7 studies) 6-14 days	LOW[a,b] due to risk of bias, imprecision	RR 1.30 (0.84 to 2.00)	75 per 1000	23 more per 1000 (from 12 fewer to 75 more)
Fatal PE	506 (4 studies) 7-70 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.15 (0 to 7.52)	4 per 1000	3 fewer per 1000 (from 4 fewer to 24 more)

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

Table 190: Clinical evidence summary: UFH versus IPCD (below knee)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with UFH versus IPCD (95% CI)
DVT	265 (2 studies) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 2.36 (0.87 to 6.44)	38 per 1000	52 more per 1000 (from 5 fewer to 209 more)
PE	265		Peto OR 1.04	8 per 1000	0 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with UFH versus IPCD (95% CI)
	(2 studies) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	(0.06 to 17)		(from 7 fewer to 109 more)

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

Table 191: Clinical evidence summary: UFH versus VKA

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with UFH versus VKA (95% CI)
DVT	197 (2 studies) time-point not reported	LOW[a,b] due to risk of bias, imprecision	RR 0.33 (0.11 to 1)	122 per 1000	82 fewer per 1000 (from 109 fewer to 0 more)
Major bleeding	100 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 38 fewer to 38 more)[d]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Could not be calculated as there were no events in the intervention or comparison group
d Risk difference calculated in Review Manager

Table 192: Clinical evidence summary: LMWH (low dose) versus no prophylaxis

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with Control	Risk difference with LMWH low dose versus no prophylaxis (95% CI)
All-cause mortality	183 (1 study) 42 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.12 (0.01 to 1.99)	23 per 1000	20 fewer per 1000 (from 22 fewer to 22 more)
DVT	183 (1 study) 42 days	LOW[a,b] due to risk of bias, imprecision	RR 0.26 (0.09 to 0.77)	159 per 1000	118 fewer per 1000 (from 37 fewer to 145 fewer)
PE	183 (1 study) 42 days	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	Peto OR 0.12 (0.01 to 1.99)	23 per 1000	20 fewer per 1000 (from 22 fewer to 22 more)
Major bleeding	183 (1 study) 42 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.93 (0.24 to 3.59)	45 per 1000	3 fewer per 1000 (from 35 fewer to 118 more)
Thrombocytopaenia	183 (1 study) 42 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 21 fewer to 21 more)[e]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

Table 193: Clinical evidence summary: LMWH (low dose; standard duration) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH low dose versus UFH (95% CI)
All-cause mortality	7018 (7 studies) 6-56 days	LOW[a,b] due to risk of bias, imprecision	RR 1.27 (0.93 to 1.73)	19 per 1000	5 more per 1000 (from 1 fewer to 14 more)
DVT	3045 (5 studies) 6-30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.91 (1.22 to 3.00)	18 per 1000	17 more per 1000 (from 4 more to 37 more)
PE	6836 (7 studies) 6-30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.87 (0.41 to 1.83)	4 per 1000	1 fewer per 1000 (from 3 fewer to 4 more)
Major bleeding	6694 (7 studies) 5-30 days	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.73 (0.49 to 1.11)	52 per 1000	14 fewer per 1000 (from 26 fewer to 6 more)
Fatal PE	5848 (5 studies) 6-30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.75 (0.54 to 5.71)	1 per 1000	1 more per 1000 (from 1 fewer to 6 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment because heterogeneity, I^2=55%, p=0.04, unexplained by subgroup analysis.

Table 194: Clinical evidence summary: LMWH (standard dose; standard duration) versus no prophylaxis/mechanical

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH standard dose versus no prophylaxis (95% CI)
All-cause mortality	80 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.01 to 2.26)	49 per 1000	42 fewer per 1000 (from 48 fewer to 55 more)
DVT	130 (2 studies) 7-30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.35 (0.1 to 1.2)	136 per 1000	89 fewer per 1000 (from 123 fewer to 27 more)
PE	130 (2 studies) 14-30 days	VERY LOW[a,b,c] due to risk of bias, imprecision	Peto OR 0.14 (0 to 7.17)	15 per 1000	13 fewer per 1000 (from 15 fewer to 84 more)
Major bleeding	527 (5 studies) 11-30 days	LOW[a,b] due to risk of bias, imprecision	Peto OR 2.90 (0.9 to 9.34)	9 per 1000	16 more per 1000 (from 1 fewer to 67 more)

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

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

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

Table 195: Clinical evidence summary: LMWH (standard dose; standard duration) versus IPCD (undefined)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH low dose versus IPCD (95% CI)
DVT	211 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.98 (0.2 to 19.23)	9 per 1000	9 more per 1000 (from 8 fewer to 145 more)
PE	211 (1 study) 30 days	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 18 fewer to 18 more)[e]
Thrombocytopaenia	211 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.5 (0.09 to 2.7)	38 per 1000	19 fewer per 1000 (from 34 fewer to 64 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Could not be calculated as there were no events in the intervention or comparison group
e Risk difference calculated in Review Manager

Table 196: Clinical evidence summary: LMWH (standard dose; standard duration) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH standard dose versus UFH (95% CI)
All-cause mortality	2511 (5 studies) 8-30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.04 (0.60 to 1.80)	19 per 1000	1 more per 1000 (from 8 fewer to 15 more)
DVT	2856		RR 0.85	40 per 1000	6 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH standard dose versus UFH (95% CI)
	(8 studies) 7-56 days	LOW[a,b] due to risk of bias, imprecision	(0.59 to 1.24)		(from 16 fewer to 10 more)
PE	3360 (8 studies) 7-56 days	MODERATE[a] due to risk of bias	Peto OR 0.24 (0.08 to 0.73)	7 per 1000	5 fewer per 1000 (from 2 fewer to 6 fewer)
Major bleeding	3150 (8 studies) 8-30 days	LOW[a,b] due to risk of bias, imprecision	RR 1.69 (1.19 to 2.41)	28 per 1000	19 more per 1000 (from 5 more to 39 more)
Fatal PE	1002 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0.00 to 6.71)	2 per 1000	2 fewer per 1000 (from 2 fewer to 11 more)

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

Table 197: Clinical evidence summary: LMWH (high dose; standard duration) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with LMWH high dose (95% CI)
All-cause mortality	61 (1 study) 7 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 62 fewer to 62 more)[d]
DVT	61 (1 study) 7 days	LOW[a,b] due to risk of bias, imprecision	RR 0.19 (0.05 to 0.78)	355 per 1000	287 more per 1000 (from 78 fewer to 337 fewer)

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylaxis	Risk difference with LMWH high dose (95% CI)
risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs c Could not be calculated as there were no events in the intervention or comparison group d Risk difference calculated in Review Manager					

Table 198: Clinical evidence summary: LMWH (high dose; standard duration) versus UFH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH high dose versus UFH (95% CI)
All-cause mortality	43 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 87 fewer to 87 more)[d]
DVT	43 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 87 fewer to 87 more)[d]
Major bleeding	43 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	RR 5.22 (0.68 to 39.74)	50 per 1000	211 more per 1000 (from 16 fewer to 1000 more)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs c Could not be calculated as there were no events in the intervention or comparison group d Risk difference calculated in Review Manager					

Table 199: Clinical evidence summary: LMWH (low dose; standard duration) versus LMWH (standard dose; standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with LMWH low dose versus LMWH standard dose (95% CI)
All-cause mortality	2931 (2 studies) 8-30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.07 (0.7 to 1.62)	29 per 1000	2 more per 1000 (from 9 fewer to 18 more)
DVT	2853 (3 studies) 7-30 days	MODERATE[a] due to risk of bias	RR 1.98 (1.51 to 2.59)	50 per 1000	49 more per 1000 (from 26 more to 80 more)
PE	2853 (3 studies) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.15 (0.42 to 3.16)	5 per 1000	1 more per 1000 (from 3 fewer to 10 more)
Major bleeding	2966 (3 studies) 30 days	VERY LOW[a,b,c,d] due to risk of bias, inconsistency, indirectness, imprecision	RR 0.58 (0.14 to 2.41)	16 per 1000	7 fewer per 1000 (from 14 fewer to 23 more)
Fatal PE	35 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[e]	Not estimable[e]	0 fewer per 1000 (from 106 fewer to 106 more)[f]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment because heterogeneity, I2=66%, p=0.05, unexplained by subgroup analysis
d Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
e Could not be calculated as there were no events in the intervention or comparison group
f Risk difference calculated in Review Manager

Table 200: Clinical evidence summary: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)

Outcomes	No of	Quality of the	Relative effect	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	(95% CI)	Risk with Control	Risk difference with Extended duration LMWH standard dose versus standard duration LMWH standard dose (95% CI)
All-cause mortality	501 (1 study) 60 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.51 (0.13 to 1.99)	36 per 1000	18 fewer per 1000 (from 31 fewer to 36 more)
DVT	332 (1 study) 25-31 days	LOW[a,b] due to risk of bias, imprecision	RR 0.43 (0.18 to 0.89)	120 per 1000	68 fewer per 1000 (from 13 fewer to 98 fewer)
PE	332 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.01 to 2.19)	12 per 1000	10 fewer per 1000 (from 12 fewer to 14 more)
Major bleeding	928 (2 studies) up to 90 days	VERY LOW[a,b,c]= due to risk of bias, imprecision, inconsistency	Peto OR 0.83 (0.22 to 3.08)	11 per 1000	2 fewer per 1000 (from 8 fewer to 21 more)
Fatal PE	332 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.00 to 6.90)	6 per 1000	5 fewer per 1000 (from 6 fewer to 34 more)

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

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

c Downgraded by 1 increment because heterogeneity, I^2=60%, p=0.12, unexplained by subgroup analysis.

Table 201: Clinical evidence summary: LMWH (high dose; extended duration) versus LMWH (high dose; standard duration)

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Extended duration LMWH high dose versus standard duration LMWH high dose (95% CI)
All-cause mortality	488 (1 study) 90 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.29 (0.45 to 3.66)	25 per 1000	7 more per 1000 (from 14 fewer to 67 more)
DVT	488 (1 study) 28 days	LOW[a,b] due to risk of bias, imprecision	RR 0.63 (0.37 to 1.10)	121 per 1000	45 fewer per 1000 (from 76 fewer to 12 more)
PE	488 (1 study) 28 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 8 fewer to 8 more)[d]
Major bleeding	625 (1 study) 22 days	LOW[b] due to imprecision	Peto OR 1.92 (0.20 to 18.54)	3 per 1000	3 more per 1000 (from 3 fewer to 53 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Could not be calculated as there were no events in the intervention or comparison group
d Risk difference calculated in Review Manager

Table 202: Clinical evidence summary: LMWH (standard dose; extended duration) + AES (undefined) versus LMWH (standard dose; standard duration) + AES (undefined)

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with LMWH standard dose standard duration + AES	Risk difference with LMWH standard dose extended duration + AES (95% CI)
All-cause mortality	427 (1 study) 60 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.27 (0.69 to 2.36)	77 per 1000	21 more per 1000 (from 24 fewer to 104 more)
DVT	340 (1 study) 60 days	LOW[a,b] due to risk of bias, imprecision	RR 0.50 (0.26 to 0.95)	149 per 1000	76 fewer per 1000 (from 9 fewer to 110 fewer)
PE	343 (1 study) 28 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.14 (0.01 to 1.40)	17 per 1000	14 fewer per 1000 (from 17 fewer to 7 more)
Fatal PE	427 (1 study) 28 days	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[c]	Not estimable[c]	0 fewer per 1000 (from 9 fewer to 9 more)[d]

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

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

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

d Risk difference calculated in Review Manager

Table 203: Clinical evidence summary: Fondaparinux versus LMWH (standard dose; standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Fondaparinux versus LMWH standard dose (95% CI)
All-cause mortality	2858 (1 study) 32 days	LOW[a,b] due to risk of bias,	RR 0.72 (0.48 to 1.08)	39 per 1000	11 fewer per 1000 (from 20 fewer to 3 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Fondaparinux versus LMWH standard dose (95% CI)
		imprecision			
DVT	2042 (1 study) 32 days	LOW[a,b] due to risk of bias, imprecision	RR 0.72 (0.49 to 1.06)	58 per 1000	16 fewer per 1000 (from 30 fewer to 3 more)
PE	2927 (1 study) 32 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.38 (0.46 to 118.03)	0 per 1000	Not estimable[c]
Major bleeding	2858 (1 study) 5-11 days	LOW[a,b] due to risk of bias, imprecision	RR 1.43 (0.93 to 2.21)	24 per 1000	10 more per 1000 (from 2 fewer to 29 more)
Fatal PE	2927 (1 study) 32 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1 (0.2 to 4.95)	2 per 1000	0 fewer per 1000 (from 2 fewer to 8 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Could not be calculated as there were no events in the comparison group

Table 204: Clinical evidence summary: Fondaparinux + IPCD (undefined) versus IPCD (undefined)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Fondaparinux + IPCD versus IPCD (95% CI)
All-cause mortality	1285 (1 study)	LOW[b]	Peto OR 1.63 (0.55 to 4.86)	8 per 1000	5 more per 1000 (from 3 fewer to 29 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Fondaparinux + IPCD versus IPCD (95% CI)
	32 days	due to imprecision			
DVT	842 (1 study) 10 days	MODERATE[a] due to risk of bias	RR 0.31 (0.14 to 0.73)	53 per 1000	36 fewer per 1000 (from 14 fewer to 45 fewer)
PE	1285 (1 study) 32 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.36 (0.05 to 2.57)	6 per 1000	5 fewer per 1000 (from 7 fewer to 11 more)
Fatal PE	1285 (1 study) 32 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.02 (0.06 to 16.39)	2 per 1000	0 more per 1000 (from 1 fewer to 23 more)

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

Table 205: Fondaparinux versus no prophylaxis/mechanical

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Fondaparinux + IPCD versus IPCD (95% CI)
Major bleeding	1285 (1 study) 32 days	MODERATE[a] due to risk of bias	Peto OR 5.33 (1.63 to 17.45)	2 per 1000	7 more per 1000 (from 1 more to 25 more)

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

Table 206: Fondaparinux + UFH + mechanical (AES + IPCD) versus LMWH + UFH + mechanical (AES + IPCD)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH + UFH + mech	Risk difference with Fonda + UFH + mech (95% CI)
PE	258 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 2.13)	16 per 1000	14 fewer per 1000 (from 15 fewer to 17 more)
Major bleeding	298 (1 study) time-point not reported	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.88 (0.19 to 18.21)	7 per 1000	6 more per 1000 (from 6 fewer to 105 more)

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

Table 207: VKA versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with VKA versus no prophylaxis (95% CI)
DVT	96 (1 study) 7 days	LOW[a,b] due to risk of bias, imprecision	RR 0.27 (0.08 to 0.92)	229 per 1000	167 fewer per 1000 (from 18 fewer to 211 fewer)

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

35.4 Economic evidence

Published literature

Two original economic models were developed for this population in CG92.[224] Additionally, one health economic study was also identified with the relevant comparison and has been included in this review.[305] These are summarised in the health economic evidence profiles below (Table 208, Table 209 and Table 210) and the health economic evidence tables in appendix J.

An economic model was developed for this population in CG46; for both standard duration and post-discharge prophylaxis. Both these models were selectively excluded due to the availability of the more applicable model from CG92. [224] Additionally, three economic studies relating to this review question were previously included in CG46, [226] but one was excluded due to methodological limitations,[219] and the other two were selectively excluded due to the availability of more applicable evidence.[121,253] These are listed in appendix O, with reasons for exclusion given.

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

Table 208: Health economic evidence profile: LMWH (standard dose, standard duration) + AES (knee-length) vs LMWH (standard dose , standard duration) + AEs (thigh-length) vs LMWH (standard dose, standard duration)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Wade 2015[305] ([UK])	Directly applicable [(a)]	Potentially serious limitations [(b)]	- **Study design**: CUA using decision modelling - **Population**: Patients undergoing any general surgery (subgroups considered were high risk patients, medium risk patients and low risk patients). - **Interventions:** **Intervention 1:** LMWH (for duration of 7 days (standard duration). **Intervention 2:** Knee-length AES in addition to LMWH for a duration of 7 days (standard duration). **Intervention 3:** Thigh-length AES in addition to pharmacological prophylaxis (LMWH) for duration of 7 days (standard duration).	**High risk patients:** 1 (vs 3) : £176 2 (vs 3): £177 3: comparator **Intermediate risk patients:** 1 (vs 3) : £46 2 (vs 3): £76 3: comparator **Low risk patients:** 1:comparator) 2 (vs 1) : £35 3 (vs 1): £5	**High risk patients:** 1 (vs 3): 0.009 QALYs lost 2 (vs 3) : 0.007 QALYs lost 3: comparator **Intermediate risk patients:** 1 (vs 3):0.004 QALYs lost 2 (vs 3): 0.003 QALYs lost 3 : comparator **low risk patients:** 1: Comparator 2 (vs 1) : 0.002 QALYs lost 3 (vs 1): 0.002	**High risk patients:** LMWH + thigh-length AES (intervention 3) dominant (less costly and more effective) **Intermediate risk patients:** LMWH + thigh-length AES (intervention 3) dominant (less costly and more effective) **Low risk patients:** LMWH + thigh-length AES (intervention 3) cost effective (ICER: £2,632 per QALY gained vs LMWH alone [intervention 1])	The results of all scenario and sensitivity analyses were largely consistent with the base case analysis for all subgroups

Abbreviations: AES: anti-embolism stockings; CUA: cost utility analysis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; QALY: quality-adjusted life years; RCT: randomised controlled trial

a) Mixed population of all surgery types, however subgroup analysis is also presented.

b) The model did not include some relevant health outcomes; e.g. clinically-relevant non-major bleeding , minor bleeding and surgical site infection.

Table 209: Health economic evidence profile: pharmacological, mechanical or combination of prophylaxis strategies vs each other

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
National Guideline Centre 2010[224] ([UK])	Partially applicable [(a)]	Potentially serious limitations [(b)]	- **Study design:** CUA using decision analytic model based on NMAs - **Population:** Adult (18 years or older) admitted for elective abdominal surgery to hospitals in England. - **Interventions:** 1. AES 2. IPCD-FID 3. UFH+ AES 4. LMWH+ AES 5. LMWH 6. Aspirin high dose 7. UFH 8.Fondaparinux+ IPCD-FID 9.Fondaparinux 10.VKA 11.No prophylaxis 12.UFH+ Aspirin high dose	NR	NR	**Incremental net benefit:** Intervention 1: £488 Intervention 2: £464 Intervention 3: £408 Intervention 4: £348 Intervention 5: £347 Intervention 6: £314 Intervention 7: £241 Intervention 8: £127 Intervention 9: £104 Intervention 10: £75 Intervention 11: £0 Intervention 12: -£694	High- dose aspirin alone was the most cost effective strategy when the population specific pulmonary embolism relative risks were used. The results were highly sensitive to baseline risk of major bleeding and baseline risk of pulmonary embolism. For patients at lowest risk of major bleeding, combination prophylaxis is cost-effective, rather than mechanical prophylaxis alone.

Abbreviations: AES: Anti-embolism stockings; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; DVT: deep vein thrombosis; FID: foot impulse devices; HD: high dose; HIT: Heparin induced thromboembolism; ICER: incremental cost-effectiveness ratio; IPCD: intermittent pneumatic compression device; LMWH: low molecular weight heparin; MB: major bleeding; NMA: network meta-analysis; PE: pulmonary embolism; QALY: quality-adjusted life years; RCT: randomised controlled trial; UFH: unfractionated heparin; VTE: venous thromboembolism; VKA: Vitamin K antagonists.

(a) Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context. Some interventions are not included in our review protocol (aspirin (high dose))

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

Table 210: Health economic evidence profile: LMWH (post-discharge) vs no post-discharge prophylaxis

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
National Guideline Centre 2010[224] ([UK])	Directly applicable [(a)]	Potentially serious limitations [(b)]	- **Study design:** CUA using decision analytic model based on pairwise Meta-analysis - **Population:** Adult (18 years or older) admitted for elective abdominal surgery to hospitals in England ; randomised 10 to 12 days after surgery (mainly cancer surgery patients) - **Interventions:** **Intervention 1:** No post discharge prophylaxis **Intervention 2:** LMWH initiated post discharge and continued for 21 days.	NR	NR	**Incremental net benefit:** No prophylaxis**:** £0 (comparator) LMWH (post-discharge)**:** £49	The result was consistent for all deterministic sensitivity analyses. In the probabilistic sensitivity analysis, LMWH was more cost-effective in 77% of the 5000 simulations of the probabilistic sensitivity analysis. It was also found that life expectancy would have to be halved for it to no longer be cost-effective for these patients

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

(a) Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context.

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

35.5 Evidence statements

Clinical

Pairwise meta-analysis statements

Mechanical prophylaxis versus mechanical prophylaxis

AES

Two studies (n=291) evaluated the use of above knee AES compared to no prophylaxis. A clinical benefit of AES was found for DVT, and a possible clinical benefit was found for PE, although for this outcome there was very serious imprecision around the estimate. No clinical difference was found for all-cause mortality. The evidence ranged from very low to moderate quality due to risk of bias and imprecision.

One study (n=95) compared below knee AES to no prophylaxis and found a possible clinical benefit of stockings in terms of DVT. However there was very serious imprecision, and therefore the estimate is also consistent with no difference and clinical harm. The evidence was very low quality due to risk of bias and imprecision.

One study compared AES at an undefined length to no VTE prophylaxis. The evidence showed that for the outcome of DVT, there was a clinical benefit of AES. Evidence for this comparison was of moderate quality due to risk of bias.

One study (n=114) compared above knee AES with below knee AES. For the only reported outcome of DVT, there was a possible clinical harm of above knee AES, however there was very serious imprecision around the estimate and therefore was also consistent with no difference and clinical benefit. The evidence for this comparison was of very low quality due to risk of bias and imprecision.

Foot pump

One study of 66 participants evaluated the use of foot pumps compared to no prophylaxis. The evidence demonstrated a possible clinical benefit of foot pumps in terms of both all-cause mortality and DVT, however imprecision around these estimates was also consistent with no difference and in the case of mortality, also possible harm as well. The quality of evidence for this comparison ranged from low to very low due to risk of bias and imprecision.

IPCD

Four studies evaluated IPCD (below knee) versus no prophylaxis. A possible clinical benefit of IPCD was found for both DVT and fatal PE, however for both of these outcomes there was very serious imprecision around the estimate, and therefore was also consistent with no difference and clinical harm. No clinical difference was found for all-cause mortality, and there was a suggested clinical harm of IPCD in terms of PE. Again, both of these outcomes had serious imprecision around the estimate. The evidence for this comparison was very low due to risk of bias, imprecision, and for the DVT outcome, inconsistency.

One study (n=90) evaluated the use of IPCD (full leg) compared to IPCD (below knee). The evidence showed a possible clinical benefit of full leg IPCD in terms DVT and fatal PE, but a suggested clinical harm for full leg IPCD in terms of PE. Quality was very low due to risk of bias and imprecision.

Pharmacological prophylaxis versus pharmacological prophylaxis

UFH

Two studies evaluated the use UFH versus VKA in terms of DVT (n=197). A possible clinical benefit was found for UFH, however there was serious imprecision around the estimate and therefore evidence was also consistent with no difference. One study reported the outcome of major bleeding

(n=100). No clinical difference was found between UFH and VKA, however there was very serious imprecision which meant that this was also consistent with clinical benefit and clinical harm. The evidence quality ranged from low to very low due to risk of bias and imprecision.

LMWH (low dose)

One study compared LMWH at a low dose with no prophylaxis (n=183). There was a suggested clinical benefit for LMWH for all-cause mortality, DVT and PE. There was no clinical difference for major bleeding and thrombocytopaenia. Quality ranged from very low to low due to risk of bias, imprecision and for one outcome, indirectness.

LMWH at a low dose was compared to UFH. Seven studies reported the outcomes all-cause mortality, PE and major bleeding (n=6694-7018). The evidence demonstrated a possible clinical harm of LMWH for all-cause mortality, and a possible clinical harm for major bleeding. Both outcomes had serious imprecision around the estimate, and therefore were also consistent with no difference. There was no clinical difference between LWMH and UFH in terms of PE, with very serious imprecision consistent with clinical benefit and clinical harm. Five studies reported the outcomes DVT and fatal PE (n=3045-5848). Evidence from these studies showed a possible clinical harm for both outcomes, however there was serious and very serious imprecision around the estimates. The quality of the evidence ranged from very low to low due to risk of bias, imprecision and inconsistency.

LMWH at a low dose was compared to LMWH at a standard dose. Two studies reported the outcome all-cause mortality (n=2931). The evidence demonstrated a possible clinical harm of low dose LMWH, however there was very serious imprecision consistent with no difference and benefit. Three studies reported the outcomes DVT, PE and major bleeding (n=2853-2966). There was a possible clinical harm of low dose LMWH in terms of DVT, no clinical difference in terms of PE, and a possible clinical benefit of low dose LMWH in terms of major bleeding. All outcomes had very serious imprecision. One study reported the outcome fatal PE (n=35). This study demonstrated no clinical difference between the two doses of LMWH, however there was very serious imprecision consistent with both harm and benefit. Evidence for the comparison ranged from very low to moderate quality, due to risk of bias, imprecision and, for the major bleeding outcome, indirectness and inconsistency.

LMWH (standard dose)

For the comparison of LWMH (standard dose) versus UFH, eight studies reported the outcomes DVT, PE and major bleeding. There was a possible clinical benefit of LMWH for PE, no clinical difference for DVT, and a suggested clinical harm of LMWH for major bleeding. The DVT outcome had serious imprecision around the estimate consistent with benefit, whereas the major bleeding outcome demonstrated serious imprecision consistent with no difference. Five studies reported the outcome all-cause mortality. No clinical difference between LMWH and UFH was found, however there was very serious imprecision around the estimate, and therefore was consistent with clinical harm and clinical benefit. One study reported fatal PE, and found a possible clinical benefit of LMWH, however this outcome had very serious imprecision consistent with no difference and clinical harm. The evidence ranged from low to very low quality due to risk of bias, imprecision, and inconsistency.

Standard dose LMWH at an extended duration was compared to standard dose LMWH at a standard duration. One study reported the outcomes all-cause mortality, DVT, PE and fatal PE (n=332-501). A possible clinical benefit of extended duration LMWH was found for all-cause mortality, DVT, PE and fatal PE, however all outcomes had either serious or very serious imprecision around the estimate. Two studies reported the outcome major bleeding (n=928). There was no clinical difference for major bleeding, however there was very serious imprecision around the estimate consistent with both benefit and harm. The evidence ranged from very low to low quality due to risk of bias and imprecision.

LMWH (high dose)

One study evaluated LMWH at a high dose versus no prophylaxis. The evidence demonstrated a possible clinical benefit for LWMH was found for DVT. However there was serious imprecision around the estimate, and therefore evidence was also consistent with no difference. No clinical difference was found between LMWH and no prophylaxis in terms of all-cause mortality, however again there was very serious imprecision around the estimate. The evidence was of low quality due to risk of bias and imprecision.

For the comparison of LMWH at a high dose versus UFH, one study of 43 participants reported the outcomes all-cause mortality, DVT and major bleeding. There was no clinical difference between the two pharmacological prophylaxis methods for the all-cause mortality and DVT outcomes, although there was very serious imprecision around the estimate for both outcomes, which therefore were also consistent with benefit and harm. There was a possible clinical harm of LMWH in terms of major bleeding, with very serious imprecision around the estimate. The quality of the evidence was very low for all outcomes due to risk of bias and imprecision.

One study compared high dose LMWH at an extended duration versus high dose LMWH at a standard duration (n=488-625). A possible clinical benefit of extended duration LMWH was found for DVT, however there was serious imprecision around the estimate and therefore was also consistent with no difference. A possible clinical harm was found for all-cause mortality and major bleeding however there was very serious imprecision consistent with no difference and benefit. There was no clinical difference for PE, with very serious imprecision consistent with both benefit and harm. The evidence ranged from very low to low quality due to risk of bias and imprecision.

Fondaparinux

One study compared fondaparinux to LMWH at a standard dose (n=2042-2927). A possible clinical benefit was found for fondaparinux in terms of all-cause mortality, and DVT. Both outcomes had serious imprecision around the estimate and so were also consistent with no difference. A possible clinical harm was found for PE and major bleeding. Very serious imprecision around the estimate for PE meant that it is also consistent with no difference and benefit, and serious imprecision around the estimate for major bleeding meant that the outcome is also consistent with no difference. No clinical difference was found for fatal PE, with very serious imprecision. The evidence ranged from low to very low quality due to risk o bias and imprecision.

VKA

One study compared VKA with no prophylaxis (n=96). For the outcome of DVT, there was a possible clinical benefit of VKA, however there was serious imprecision around the estimate and therefore this was also consistent with no difference. The evidence was low quality due to risk of bias and imprecision.

Mechanical prophylaxis versus pharmacological prophylaxis

One study compared above knee AES with UFH (n=97). There was a possible clinical benefit of AES in terms of fatal PE, however there was very serious imprecision around the estimate consistent with no difference and harm. The evidence was very low quality due to risk of bias and imprecision.

One study compared below knee AES with UFH (n=159). No clinical difference was found for both all-cause mortality and PE, with very serious imprecision consistent with both benefit and harm. The evidence was of very low quality due to risk of bias, imprecision and, for the PE outcome, indirectness.

One study of 100 participants compared electrical stimulation with UFH. There was a possible clinical harm of electrical stimulation in terms of DVT, however there was very serious imprecision consistent with benefit and no difference. The evidence was of very low quality due to risk of bias and imprecision.

One study compared full leg IPCD versus VKA (n=100). A possible clinical harm of ICPD was found for DVT and PE. For both outcomes there was very serious imprecision around the estimate consistent with benefit and no difference. There was no clinical difference for all-cause mortality, again with very serious imprecision. The evidence was very low quality due to risk of bias and imprecision.

Pharmacological prophylaxis versus mechanical prophylaxis

UFH was compared to no prophylaxis/mechanical prophylaxis. Twelve studies reported the outcome DVT (n=1991), and the evidence demonstrated a clinical benefit for UFH. Ten studies reported the outcome PE (n=897). There was a possible clinical benefit of UFH, however there was serious imprecision, and was therefore also consistent with no clinical difference. Seven studies reported the outcome major bleeding (n=725). This demonstrated a possible clinical harm of UFH, with serious imprecision consistent with no difference. Four studies reported the outcomes all-cause mortality and fatal PE (n=393-506). There was a possible clinical benefit of UFH for both outcomes, however both outcomes also had very serious imprecision around the estimate and were consistent with no difference and clinical harm. The evidence ranged from very low to moderate quality due to risk of bias and imprecision.

Standard dose LMWH was compared to no prophylaxis/mechanical prophylaxis. One study reported the outcome all-cause mortality (n=80). There was a possible clinical benefit of LMWH for this outcome, however there was very serious imprecision around the estimate and so this was also consistent with harm and no difference. Two studies reported DVT and PE (n=130). There was a possible clinical benefit of LMWH for both outcomes, however there was serious and very serious imprecision around the estimates, consistent with no difference, and no difference and clinical harm. Five studies reported the outcome major bleeding (n=527). The evidence demonstrated a possible clinical harm of LMWH for this outcome, however there was serious imprecision which was also consistent with no difference. The evidence was very low to low quality due to risk of bias and imprecision.

One study compared fondaparinux to no prophylaxis/mechanical prophylaxis (n=1285). There was a clinical harm of fondaparinux in terms of DVT. No other outcomes were reported. The evidence was high quality.

Two studies compared UFH and below knee IPCD (n=265). A possible clinical harm was found for UFH in terms of DVT, however there was serious imprecision around the estimate and therefore was also consistent with no difference. No clinical difference was found for PE, however there was very serious imprecision around the estimate consistent with both benefit and harm. The evidence ranged from very low to low quality due to risk of bias and imprecision.

One study compared standard dose LMWH to IPCD at an undefined length (n=211). The evidence demonstrated a possible clinical harm of LMWH in terms of DVT, however there was very serious imprecision around the estimate consistent with no difference and benefit. There was no clinical difference in terms of PE, with very serious imprecision consistent with both benefit and harm. For the outcome of thrombocytopaenia, a possible clinical benefit of LWMH was found, however there was also very serious imprecision consistent with no difference and harm. The evidence was very low quality due to risk of bias and imprecision.

Combination prophylaxis versus combination prophylaxis or single-prophylaxis agents

AES

One study compared below knee AES in combination with UFH to below knee AES alone (n=163). There was no clinical difference between the interventions for both all-cause mortality and PE, however there was very serious imprecision for both outcomes consistent with both benefit and harm. The evidence was very low quality due to risk of bias and inconsistency.

Above knee AES in combination with UFH was compared to UFH alone. One study reported the outcomes all-cause mortality and fatal PE (n=160-176). A possible clinical harm was found for the combination intervention in terms of all-cause mortality, however there was very serious imprecision around the estimate, and therefore this was also consistent with no difference and benefit. A possible clinical benefit was seen for the combination in terms of fatal PE, however again there was very serious imprecision consistent with no difference and harm. Two studies reported the outcomes DVT and PE (n=336). There was a clinical benefit of the combination intervention in terms of DVT, and a possible clinical benefit in terms of PE, although this outcome estimate had very serious imprecision and was consistent with no difference and harm. The evidence ranged from very low to moderate quality due to risk of bias and imprecision.

One study compared below knee AES in combination with UFH to UFH alone (n=174). The evidence showed no clinical difference for all-cause mortality or PE. Both outcomes had very serious imprecision around the estimate and therefore were also consistent with both benefit and harm. The evidence was very low quality due to risk of bias, imprecision and, for the PE outcome, indirectness.

One study compared the combination of above knee AES and full leg IPCD with above knee AES alone (n=77). There was a possible clinical benefit of the combined interventions for DVT, however there was very serious imprecision around the estimate and this was therefore also consistent with no difference and harm. There was no clinical difference in terms of PE, however there was very serious imprecision consistent with both benefit and harm. The evidence was very low quality due to risk of bias and imprecision.

One study compared AES at an undefined length in combination with full leg IPCD to AES alone (n=108). There was a possible clinical benefit of the combined interventions in terms of DVT, however there was serious imprecision consistent with no difference. There was no clinical difference in terms of PE, with very serious imprecision around the estimate, consistent with both harm and benefit. The evidence ranged from very low to low quality due to risk of bias and imprecision.

One study compared AES at an undefined length in combination with full leg IPCD to UFH alone (n=100). There was a possible clinical benefit of the combined intervention in terms of DVT, however there was very serious imprecision around the estimate and therefore was also consistent with no difference and harm. No other outcomes were reported. The evidence was very low quality due to risk of bias and imprecision.

One study compared AES at an undefined length in combination with full leg IPCD to electrical stimulation alone (n=100). There was a possible clinical benefit of the combined intervention in terms of DVT, however there was serious imprecision around the estimate consistent with no difference. No other outcomes were reported. The evidence was low quality due to risk of bias and imprecision.

Foot impulse device

One study compared the combination of FID, below knee IPCD and low dose LMWH to the combination of FID and below knee IPCD. A possible clinical benefit was found for both DVT and PE, however with very serious and serious imprecision around the estimates. No clinical difference was found in terms of thrombocytopaenia, however there was very serious imprecision consistent with both benefit and harm. The evidence was very low to low quality due to risk of bias , imprecision and, for the DVT outcome, indirectness.

IPCD

Two studies compared IPCD at an undefined length in combination with standard dose LMWH with IPCD at an undefined length alone (n=334). The evidence showed a clinical benefit of the combination intervention in terms of DVT. There was no clinical difference in terms of PE, however

there was very serious imprecision around the estimate for this outcome, and therefore was consistent with both benefit and harm. The evidence ranged from very low to low quality due to risk of bias, imprecision, and for the PE outcome, indirectness.

LMWH

One study compared standard dose and extended duration LMWH in combination with AES at an undefined length, to standard dose and standard duration LMWH in combination with AES at an undefined length (n=343-427). There was a possible clinical harm of the extended duration LMWH combination in terms of all-cause mortality, however there was very serious imprecision around the estimate and so this was also consistent with benefit and no difference. There was a possible clinical benefit for both DVT and PE. Both outcomes also had serious and very serious imprecision around the estimate. There was no clinical difference in terms of fatal PE. This outcome had very serious imprecision around the estimate consistent with both harm and benefit. The evidence ranged from very low to low quality due to risk of bias and imprecision.

Fondaparinux

One large study compared fondaparinux in combination with IPCD at an undefined length, to IPCD at an undefined length alone (n=842-1285). There was a possible clinical harm of the fondaparinux + IPCD combination in terms of all-cause mortality, however there was very serious imprecision around the estimate and therefore this was also consistent with benefit and no difference. There was a clinical benefit of the combined intervention in terms of DVT, and a possible benefit in terms of PE, although this was also consistent with no difference and clinical harm. There was no clinical difference in terms of fatal PE, although due to very serious imprecision around the estimate this was also consistent with both benefit and harm. The evidence ranged from very low to moderate quality due to risk of bias and imprecision.

One study compared fondaparinux in combination with UFH and mechanical prophylaxis (AES and IPCD), to standard dose LMWH in combination with UFH and mechanical prophylaxis (AES and IPCD) (n=258-298). There was a possible clinical benefit of the fondaparinux combination intervention in terms of PE, however there was very serious imprecision consistent with no difference and clinical harm. There was a possible clinical harm in terms of major bleeding, however there was very serious imprecision around the estimate, and therefore was also consistent with no difference and benefit. The evidence was very low quality due to risk of bias and imprecision.

Network meta-analysis statements

DVT (symptomatic and asymptomatic)

48 studies were included in the network meta-analysis (NMA) for the outcome of DVT (symptomatic and asymptomatic), involving 22 treatments. Treatments included no VTE prophylaxis, pharmacological and mechanical interventions as single agents as well as combination interventions of both pharmacological and mechanical interventions. Results from the network meta-analysis presented LMWH at a standard dose for a standard duration initiated post-operatively in combination with IPCD, fondaparinux in combination with IPCD, and AES (above-knee) in combination with IPCD (full leg) as the most clinically effective interventions in terms of the outcome of DVT (symptomatic and asymptomatic). The least clinically effective interventions were no prophylaxis, VKA and LMWH at a low dose for a standard duration initiated pre-operatively. One inconsistency was identified when relative risk values from pairwise meta-analyses were compared with relative risk values from the NMA. There was also a considerable amount of uncertainty around the rank-point estimates with considerably wide credible intervals.

PE

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

Major bleeding

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

Economic

- One cost-utility analysis found that for VTE prophylaxis:
  - In low risk general surgery patients, LMWH (standard dose, standard duration) + thigh-length AES was cost effective compared to LMWH (standard dose, standard duration) alone (ICER: £2,632 per QALY gained)
  - In intermediate and high risk general surgery patients, LMWH (standard dose, standard duration) + thigh-length AES was dominant (less costly and more effective) compared to LMWH (standard dose, standard duration) alone

  This analysis was assessed as directly applicable with potentially serious limitations
- One cost-utility analysis found that in people admitted for general surgery AES was the most cost-effective intervention (having the highest incremental net monetary benefit [INMB]) compared to no prophylaxis (INMB: £488). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that post-discharge LMWH (standard dose) was cost effective (INMB: £49) compared to no post-discharge prophylaxis in patients admitted for general surgery. This analysis was assessed as directly applicable with potentially serious limitations.

35.6 Recommendations and link to evidence

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

	1.5.38 Start mechanical VTE prophylaxis on admission for people undergoing abdominal surgery. Choose either: • **anti-embolism stockings or** • **intermittent pneumatic compression. [2018]** **Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [2018]** **1.5.39 Add pharmacological VTE prophylaxis for a minimum of 7 days for people undergoing abdominal surgery whose risk of VTE outweighs their risk of bleeding, taking into account individual patient factors and according to clinical judgement. Choose either:** • **LMWH[aa] or** • **fondaparinux sodium[bb]. [2018]** **1.5.40 Consider extending pharmacological VTE prophylaxis to 28 days postoperatively for people who have had major cancer surgery in the abdomen. [2018]**
Research recommendation	**None**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge), pulmonary embolism (symptomatic and asymptomatic) (up to 90 days from hospital discharge), fatal PE (up to 90 days from hospital discharge), and major bleeding (up to 45 days from hospital discharge) as critical outcomes. The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), heparin-induced thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	Sixty-seven randomised controlled trials were included in this review. Sixty-two of these were included in the previous guideline (CG92). Five new studies were added to the review. A total of thirty-nine comparisons were included in this review, evaluating the use of pharmacological (UFH, LMWH, VKA and fondaparinux) and mechanical (AES, IPCD, foot pump, FID and electrical stimulation) interventions for VTE prophylaxis. For the majority of evidence in this review, the quality ranged from a GRADE rating of moderate to very low. This was due to a lack of blinding, presence of selection bias, incomplete outcome reporting due to the high number of drop outs in some

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

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

	included studies, and use of inadequate or unreported method of measurement, resulting in a high or very high risk of bias rating. Furthermore, much of the evidence in the review had serious or very serious imprecision, leading to further downgrading to the quality of evidence. A high quality GRADE rating was seen for one outcome, in the fondaparinux versus no prophylaxis/mechanical prophylaxis comparison, for the DVT outcome.
Trade-off between clinical benefits and harms	The committee noted that the review contains both open and laparoscopic surgery populations, and that these populations were likely to have different mobilisation times and associated risks. The committee discussed creating separate recommendations for these populations but recognised that it would be difficult to align a distinction in recommendations in line with the risk assessment recommendations, given that not all laparoscopic procedures are under 90 minutes, and given the fact that many of the included studies did not separate the two populations as they either used a mix of laparoscopic and open surgery procedures, or did not specify the type of procedure used. **Mechanical prophylaxis** The committee noted that there was no evidence for foot impulse devices as a standalone intervention and therefore a positive recommendation for the use of this intervention for VTE prophylaxis could not be made. The committee also discussed the evidence for the use of AES. It was considered that while there was no convincing evidence that above knee AES was better than below knee, the economic evidence suggested a slight benefit for above knee AES. Therefore, the committee agreed there was insufficient evidence to specify one particular option of above or below knee AES in the recommendations. In terms of IPCD the committee discussed the practical considerations that need to be taken into account with respect to mobilising the patient. IPCD are usually used only during the surgery. Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a patient is mobile. **Pharmacological prophylaxis** The committee considered the evidence for pharmacological prophylaxis. The committee noted that there was evidence to support LMWH and fondaparinux as being better than no prophylaxis. However there was not sufficient evidence to determine whether LMWH was better than fondaparinux. For prevention of DVT the evidence suggested that pharmacological prophylaxis (LMWH or fondaparinux) in combination with IPCD may be of most clinical benefit. The network meta-analysis (NMA) conducted showed that combination prophylaxis strategies with pharmacological and mechanical interventions are more clinically beneficial in terms of reducing DVT. These combination strategies had higher rankings compared to pharmacological or mechanical interventions as standalone interventions, particularly LMWH at a standard dose for a standard duration initiated post-operatively in combination with IPCD which was ranked as the most clinically effective prophylaxis in the NMA for DVT. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials was between 7 and 10 days. The committee agreed this should be extended to 28 days for cancer surgery because the evidence identified was for this duration.
Trade-off between net clinical effects and costs	Two economic studies were included in this review. One is an economic evaluation recently published as part of an HTA funded study. This was assessed as directly applicable with minor limitations. The other was the economic model previously developed for CG92 which covered two comparisons; one for standard duration prophylaxis options and the second for post-discharge prophylaxis. The model comparing standard duration prophylaxis options was assessed as partially applicable with potentially serious limitations. The model for post-discharge prophylaxis was assessed as directly applicable with potentially serious limitations. Additionally, four studies were selectively excluded; one was excluded due to

	methodological limitations, three (including the model developed for CG46) were selectively excluded due to the availability of the more applicable included studies. The first of the two included studies was an economic model that compared above and below knee AES; each combined with LMWH (standard dose and standard duration), vs LMWH alone. The results were presented for three levels of baseline risk of VTE: high, intermediate and low. For people at high or intermediate risk of VTE, LMWH + thigh-length AES was the dominant option. For people at low risk, LMWH + thigh-length AES was the cost effective option with an ICER of £2,632 per QALY gained compared to LMWH alone. Two models were developed in CG92. The first was for standard duration prophylaxis and included the following interventions: AES, IPCD-FID, UFH (standard dose)+AES, LMWH (standard dose)+ AES, LMWH (standard dose), Aspirin (high dose), UFH (standard dose), Fondaparinux+ IPCD-FID, Fondaparinux, VKA (variable dose), UFH (standard dose) + Aspirin (high dose), and no prophylaxis. The committee noted that not all of these interventions are still relevant to current practice (for example aspirin [high dose] and VKA). Mechanical prophylaxis with either AES or IPCD were the most cost effective options in the base case analysis with INMB of £488 and £464 respectively. However in a two-way sensitivity analysis that varied the baseline risk of PE and MB, combined prophylaxis of LMWH+ stocking was the most cost-effective option for high baseline risk of PE and low risk of major bleeding. The second model compared post-discharge prophylaxis with LMWH with no prophylaxis. The results showed that extending the duration of LMWH prophylaxis to continue post-discharge was cost effective compared to no prophylaxis with an INMB of £49. The committee considered the economic evidence presented, alongside the clinical evidence. The committee noted that, in line with CG92 recommendation, combined prophylaxis for people at high risk of VTE is the most cost effective option. This was supported by the newly published HTA report that stratified surgical patients according to their level of VTE risk; where combined prophylaxis was the most cost effective option. The committee considered the recent clinical evidence and determined that both LMWH and fondaparinux were better compared to no prophylaxis; however, no clear conclusion could be made in terms of superiority of one over the other. However, as low quality clinical evidence for the DVT outcome suggested superiority of fondaparinux, the committee considered that this would justify the increased cost, and the choice of either as pharmacological prophylaxis options should be made based on the baseline bleeding risk. The committee discussed whether the evidence was enough to recommend either knee or thigh length AES. The economic evidence supported the cost effectiveness of combined prophylaxis that includes thigh length AES, however the committee noted that thigh length AES are less convenient for people to wear and are more difficult to fit. Hence, the committee agreed that the choice of the length of stocking should be made taking into account the preference of the individual and his/her ability to adhere to wearing them. No studies were identified that compared thigh versus knee length for IPCD, so the committee considered that, similar to AES, the choice of the length should be based on preference, likelihood of adherence and ease of fitting. The committee also discussed the duration of prophylaxis and noted that the economic model developed for CG92 supported extending the duration of prophylaxis for those who are at increased risk of VTE. These were primarily people undergoing surgeries for cancer. For this population, continuing LMWH post discharge was found to be more cost effective than no post-discharge prophylaxis.
Other considerations	None.