16 Acutely ill medical patients admitted to hospital

16.1 Introduction

Many medical patients have more than one risk factor for VTE. Apart from being an older cohort, other risk factors reported include previous VTE, cancer, stroke, heart failure, chronic obstructive airways disease, sepsis and bed rest. At the time the previous guideline (CG92) was written the uptake of thromboprophylaxis in medical patients was poor. Following the publication of CG92 with the details of the National VTE Risk Assessment Tool, it is now estimated that 73% of medical patients receive VTE prophylaxis (NHS Safety Thermometer Data – March 2016 to March 2017, published April 12, 2017; accessed 15 August 2017).

16.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for acutely ill medical patients admitted to hospital?

For full details see review protocol in appendix C.

Table 86: PICO characteristics of review question

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

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	• Vitamin K Antagonists:
	  ○ warfarin (variable dose only)
	  ○ acenocoumarol (all doses)
	  ○ phenindione (all doses)
	• Fondaparinux (all doses)*
	• Apixaban (all doses)*
	• Dabigatran (all doses)*
	• Rivaroxaban (all doses)*
	• Aspirin (up to 300mg)*
	
	*off-label

Comparison(s)	Compared to: • Other VTE prophylaxis treatment • No VTE prophylaxis treatment • Placebo Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Low versus high dose for LMWH only Standard versus extended duration prophylaxis. Extended duration = extended beyond discharge
Outcomes	Critical outcomes: • All-cause mortality (up to 90 days after line removed) • Deep vein thrombosis (DVT) (symptomatic and asymptomatic) (7-90 days after line removed). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) • Pulmonary embolism (PE) (7 - 90 days after line removed). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE • Major bleeding (up to 45 days after line removed). 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 • Fatal PE (up to 90 days after line removed). 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 after line removed). 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 (up to 90 days after line removed) • Heparin-induced thrombocytopenia (HIT) (duration of study) Technical complications of mechanical interventions (duration of study)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.

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16.3 Clinical evidence

Twenty studies describing seventeen trials were included in the review. Nine studies [35 43 71 94 98 100 101 108 169] were previously included in the previous guideline (CG92) and eleven studies [36 60 66 81 82 87 117 160 184 172 173] were added in the update. These are summarised in **Table 87** below. Evidence from these studies is summarised in the clinical evidence summary tables below. See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

One Cochrane review [6] was identified which looked at heparin for the prevention of venous thromboembolism in acutely ill medical patients, however the review protocol differed slightly and the Cochrane could therefore not be included in full.

Summary of included studies

Table 87: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Cohen 2006 [35]	Intervention (n= 429): Fondaparinux, 2.5 mg in 0.5 ml saline given subcutaneously once daily. Start time: within 48 hours of admission. End time: 1-13 days (median 7 days) Comparison (n= 420): Placebo, 0.5 ml isotonic saline subcutaneously given once daily Start time: within 48 hours of admission End time: 1-13 days (median 7 days) Concomitant treatment: AES and physiotherapy were allowed (no information about how many used this)	n=849 Older people hospitalised for acute medical conditions Congestive heart failure (25%) acute respiratory distress (19.7%), acute infectious or inflammatory disease (25.2%) (as reported in CG92) Age (mean): 74.7 years Gender (male to female ratio): 1:1.36 35 centres in 8 countries (no further information about countries)	All-cause mortality (30 days) Fatal PE (30 days): confirmed by autopsy or no other explainable reason DVT (symptomatic and asymptomatic) (15 days): confirmed by venography Symptomatic PE (30 days): confirmed by high probability lung scan, pulmonary angiography or helical computed tomography Major bleeding (15 days): bleeding in a critical location, bleeding leading to surgical intervention, overt bleeding associated with a drop in haemoglobin concentration of ≥20 g/l or leading to transfusion of 2 or more units of red blood cells	Included in CG92
Cohen 2013 [36]	Intervention (n=4050): Rivaroxaban, 10mg	n= 8101 People hospitalised	All-cause mortality (35 days)	New study

Study	Intervention and comparison	Population	Outcomes	Comments
	once daily subcutaneously for 35±4 days. Subcutaneous placebo given for 10±4 days Comparison (n=4051): LMWH, enoxaparin 40 mg (standard dose) once daily, subcutaneously for 10±4 days. Oral placebo was given for 35±4 days	for acute medical conditions. Infectious disease 45.5%; Heart failure 32.4%; Respiratory insufficiency 28%; Ischaemic stroke 17.3%; Active cancer 7.3%; Inflammatory or rheumatic disease 3.8%; ≥ 2 medical conditions 31% Age (median): 71 years Gender (male to female ratio): 1.18/1 Multicenter, 556 sites in 52 countries (no further details about countries involved in the study)	DVT (symptomatic and asymptomatic) (35 days): definition not reported PE (35 days): definition not reported Major bleeding (35 days): Bleeding leading to a ≥2 g/dl fall in hemoglobin or a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding into a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) or bleeding leading to death	Combined asymptomatic proximal DVT and symptomatic proximal or distal DVT
Dahan 1986 [43]	Intervention (n=135): LMWH, enoxaparin, 60 mg (high dose) in a volume of 0.3 ml started on admission and continued for 10 days. Comparison (n=135): Placebo (no further details reported)	n=270 Older people hospitalised for acute medical conditions Medical conditions: heart failure 19%, respiratory diseases 22%, ischaemic stroke 18%, malignant diseases 13.5%, diabetes 4.6%, depression 3.9%, syncope 5%, infection 4.2%, neurologic diseases 2.7%, joint diseases 2.7%, hepatic or biliary diseases 1.5%, miscellaneous 3.1% Age: >65 years; mean: 80.1 years Gender (male to female ratio): 1.6:1	All-cause mortality (10 days) DVT (symptomatic and asymptomatic) (10 days): diagnosed by fibrinogen uptake test Fatal PE (10 days): diagnosed by autopsy	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
		France		
Goldhaber 2011 [60]	Intervention (n=3255): Apixaban, 2.5 mg twice daily administered orally. Received daily injections of a placebo for a minimum of 6 days. Duration: 30 days. Comparison (n=3273): LMWH, enoxaparin 40 mg (standard dose), administered subcutaneously once daily during their stay in the hospital, for a minimum of 6 days.	n=6528 People hospitalised for acute medical conditions with congestive heart failure (39%), acute respiratory failure (37.1%), infection (without septic shock) (22.2%), acute rheumatic disorder (1.2%), or inflammatory bowel disease (0.8%) and had an expected hospital stay of at least 3 days. Age (mean): 67.5 years Gender (male to female ratio): 1:1.04 Multicentre , 302 centres in 35 countries (no further details about countries involved in the study)	All-cause mortality (30 days): PE (60 days): confirmed by with the use of systematic bilateral compression ultrasonography Major bleeding (30 days): fatal or overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of 2 g or more per deciliter over a 24-hour period; transfusion of 2 or more units of packed red cells; or intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding, bleeding that occurred in an operated joint that required reoperation or intervention, or intramuscular bleeding with the compartment syndrome. Clinical relevant non-major bleeding (30 days): acute, clinically overt bleeding that did not meet the criteria for classification as a major bleeding event but did meet at least one of the following criteria: epistaxis that required medical attention or persisted for 5 minutes or more, gastrointestinal bleeding containing frank blood or coffee-ground material that tested positive for blood, endoscopically confirmed bleeding, spontaneous hematuria or hematuria persisting for 24 hours or more after urinary-tract catheterization, unusual	New study

Study	Intervention and comparison	Population	Outcomes	Comments
			bruising, radiographically confirmed hematoma, or hemoptysis.	
Harenberg 1996 [71]	Intervention (n=983): LMWH, nadroparin 36 mg (3100IU of antiXa), plus two placebo injections, 3 times daily, at 8 hour intervals Start time: within 12 hours of admission to hospital End time: 11 days Duration: 10 days Comparison (n=985): UFH, 5000IU subcutaneously given, 3 times daily at 8 hour intervals Start time: within 12 hours of admission to hospital End time: 11 days Duration: 10 days	n= 1968 People who have been hospitalised and are bed ridden, bed rest >10 days Main diagnosis: cardiac insufficiency 15%, cerebrovascular diseases 14.4%, coronary heart disease 13.7%, cancer 6.1%, diabetes 5.3%, gastrointestinal or nephrology disease 4.2%, chronic obstructive lung disease 4.42%, pneumonia or infections 2.13% Age (mean): 70.5 years Gender (male to female ratio): 1:1.8 Germany	All-cause mortality (time-point not reported) Fatal PE (time-point not reported): confirmed by perfusion scintigraphy, additional angiography or ventilation scintiscan performed if results were low probability defects PE (symptomatic) (time-point not reported): confirmed by perfusion scintigraphy, additional angiography or ventilation scintiscan performed if results were low probability defects Major bleeding (time-point not reported): no definition reported	Included in CG92
Hull 2010 [81]: EXCLAIM study	Intervention (n= 2975): LMWH, extended enoxaparin 40 mg/d (standard dose), subcutaneously given for 10 ± 4 days, then further course of enoxaparin for 28 ± 4 days. Comparison (n=2988): Placebo. Received enoxaparin subcutaneously 40 mg/d (standard dose) for 10 ± 4 days also.	n=5963 People hospitalised for acute medical conditions with recent reduced mobility, requiring total bed rest or being sedentary without bathroom privileges or with bathroom privileges. Acute infection without septic shock 33.2%; Acute respiratory insufficiency 30.3%;	All-cause mortality (90 days) PE (asymptomatic and symptomatic) (90 days): confirmed using computed tomography or ventilation–perfusion lung scanning Fatal PE (90 days): no definition reported	New study

Study	Intervention and comparison	Population	Outcomes	Comments
		Heart failure 18.7%; Post-acute ischaemic stroke 6.6%; Acute rheumatic disorders 2.7%; Active cancer 1.6%; Fracture 0.7%; Multiple diagnoses 0.6%; Active inflammatory bowel disease 0.3% Age (mean±SD): 67.9 ± 12.1 Gender (male to female ratio): 1:1 Multiple countries, 370 hospitals across 20 countries (no further details about countries involved in the study)		
Ishi 2013 [82]	Intervention (n=44): LMWH, enoxaparin 40mg (standard dose) subcutaneously given once daily. Continued until person became ambulant and ready for discharge. Comparison (n=48): UFH, 5000 IU subcutaneously given twice daily. Continued until person became ambulant and ready for discharge.	n=92 People hospitalised for acute medical conditions requiring at least 3 days of ICU stay or same duration non-ambulatory care in wards. Stroke 19.9%, cardiological dysfunction 4.8%, sepsis 11.7%, toxicological causes 26.3%, multisystem disorder 13%, others 15.2% Age (mean) : 54.4 years Gender (male to female ratio): 2.4:1 India	Major bleeding (time-point not reported): definition not reported) Heparin-induced thrombocytopenia (time-point not reported): not reported)	New study
Kakkar 2011 [87]	Intervention (n=4174): LMWH, enoxaparin 40	n=8319	All-cause mortality (90 days)	New study

Study	Intervention and comparison	Population	Outcomes	Comments
	mg (standard dose) once daily plus AES (knee-high) that provided graduated pressure from 15 mm Hg (at the ankle) to 10 mm Hg (at the knee).Duration: 10±4 days Comparison (n=4145): AES, knee-high, that provided graduated pressure from 15 mm Hg (at the ankle) to 10 mm Hg (at the knee) Placebo, received a subcutaneous injection with placebo (0.9% saline), once daily	People hospitalised for acute medical conditions Heart failure 31%; Severe systemic infection 57%; Active cancer 4.4%; Heart failure and severe systemic infection 6.2%; Heart failure and active cancer 0.2%; Severe systemic infection and active cancer 1.3%; Heart failure, severe systemic infection and active cancer 0.1%; None of the above 0.6%. Age (mean): 65.5 years Gender (male to female ratio): 1.7:1 Multicentre, 193 sites in China, India, Korea, Malaysia, Mexico, the Philippines, and Tunisia	Major bleeding (8 days): A overt bleeding associated with one of the following: death; the need for transfusion of at least 2 units of packed red cells or whole blood; a fall in the hemoglobin level of 20 g or more per liter; the requirement for a major therapeutic intervention (e.g., surgery) to stop or control bleeding; or a bleeding site that was retroperitoneal, intracranial, or intraocular. Clinically relevant non-major bleeding (8 days): defined as a non-major hemorrhage leading to discontinuation of the study drug or to hospitalization.	
Kleber 2003 [94]	Intervention (n=332): LMWH, enoxaparin 40 mg (standard dose), subcutaneously given once daily Start time: on enrolment day Duration: 10±2 days Comparison (n=333): UFH, 5000IU 3 times daily, subcutaneously Start time: on enrolment day Duration: 10±2 days Concomitant treatment: People on	n=665 People hospitalised with heart failure (50%) and respiratory disease (50%), confined to bed >2/3 of the time Age (mean± SD): 70±14 years Gender (male to female ratio): 1.1:1 Germany	All-cause mortality (time-point not reported) Fatal PE (time-point not reported): confirmed by autopsy PE (symptomatic) (time-point not reported): confirmed by perfusion scintigram) DVT (symptomatic and asymptomatic) (time-point not reported): confirmed by: patients with positive D dimer or fibrin monomer test underwent bilateral venography or	Included in CG92

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Study	Intervention and comparison	Population	Outcomes	Comments
	anticoagulants or platelet inhibitors, or NSAIDS. Heart failure patients allowed 100 mg aspirin. AES applied up to 20% of patients in each treatment group		autopsy Major bleeding (time-point not reported): retroperitoneal or intracranial bleeding, overt bleeding with haemoglobin	
Lechler 1996 [98]	Intervention (n=477): LMWH, enoxaparin 40mg (standard dose), daily and 2 placebo injections (isotonic mannitol solution) (total of 3 injections daily) All injections were 0.2 ml Start time: within 24 hours of admission Duration: 7 days Comparison (n=482): UFH, 5000IU 3 times daily subcutaneously given.	n= 959 People hospitalised for acute medical conditions who are immobile Conditions including: cardiovascular diseases, endocrinologic diseases, respiratory diseases, gastrointestinal and urogenital diseases, central nervous diseases, cancer, bone diseases, skin diseases (percentages not reported) Age (mean± SD): 74±13 years Gender (male to female ratio): 1:1.64 Austria and Germany	All-cause mortality (not reported) PE (symptomatic) (time-point not reported): confirmed by: perfusion scan, angiography and autopsy in cases of death if permitted) DVT (symptomatic and asymptomatic) (time-point not reported): confirmed by duplex sonography at end of study period, or when clinically suspected. Positive cases were confirmed with phlebography Major bleeding (time-point not reported): confirmed by decrease in Hb≥2g/dl, transfusion of >2 units of blood and/or retroperitoneal or intracranial bleeding	Included in CG92
Lederle 2006 [100]	Intervention (n= 140): LMWH, enoxaparin 40 mg (standard dose), subcutaneously given daily. First injection given immediately after randomisation. Duration of treatment not reported Comparison (n=140): Placebo, identical syringes containing placebo. Duration of	n= 280 Older people (aged 60 years and over) hospitalised and admitted to medical wards, intensive care units or intermediate care Cancer 5%, cerebrovascular disease 8.6%, chronic obstructive lung disease 47.1%,	All-cause mortality (90 days) PE (symptomatic) (90 days): confirmed by ventilation perfusion scan, pulmonary angiogram or autopsy Major bleeding (time-point not reported): no definition reported Heparin-induced	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	treatment not reported	diabetes 27.9%, congestive heart failure 22.1%, myocardial infarction 25.7%, peripheral vascular disease 22% Age (mean): 71.7 years Gender (male to female ratio): 1:0 USA	thrombocytopenia (time-point not reported)	
Leizorovicz 2004 [101]	Intervention (n=1848): LMWH, dalteparin 5000 IU (standard dose), once daily for 14 days Comparison (n=1833): Placebo, once daily for 14 days Concomitant treatment: Low dose aspirin (up to 325 mg/day), ticlopidine and clopidogrel permitted	n=3681 People hospitalised for acute medical conditions, immobilised <3 days Acute congestive heart failure (NYHA class III or IV) 51%, acute respiratory failure 30%, infectious disease 37%, rheumatological disease 11%, inflammatory bowel disease 0.49% Age (mean): 68.5 years Gender (male to female ratio): 1:1.1 Multi-national (no further details about countries involved in the study)	All-cause mortality (90 days) PE (symptomatic) (90 days): no definition reported Major bleeding (21 days): no definition reported Fatal PE (21 days): confirmed by autopsy	Included in CG92
Mahe 2005 [108]	Intervention (n=1230): LMWH, nadroparin, 0.3ml (7500 AXa IU) subcutaneously started within 24 hours of hospitalisation and continued for 21 days or until discharge.	n=2474 People hospitalised for acute medical conditions who are bedridden acute cardiovascular	All-cause mortality (time-point not reported) Fatal PE (time-point not reported): confirmed by autopsy	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=1244): Placebo (not further details reported)	disease 13%, atrial fibrillation 12%, acute pulmonary disease 22%, cancer 14%, sepsis (not pulmonary) 23% Age (mean): 70.6 years Gender (male to female ratio): 1:1.47 France		
Miranda 2017 [117]	Intervention (n=46) LMWH, enoxaparin, 60mg once daily (high dose), subcutaneously given at 12pm for 14 days. Comparison (n=45): LMWH, enoxaparin, 60mg once daily (high dose), subcutaneously given at 12pm for 14 days.	n=91 Obese people hospitalised for acute medical conditions Mean BMI: 36.5 kg/m^2 acute infection 50%, acute rheumatic disorders 18%, acute respiratory failure 10.5%, acute congestive heart failure 9%, combined indications 14% Age (mean): 71 years Gender (male to female ratio): 1:1.2 France	All-cause mortality (14 days) Major bleeding (14 days): defined as fatal, intracranial or retroperitoneal haemorrhage, necessity of blood transfusion (2 units) or decrease of haemoglobin level greater than 2g/dL. Thrombocytopenia (14 days)	New study
Riess 2010 [160] CERTIFY trial (Haas 2011 [66] – cancer subgroup; Schellong 2011 [172] – older adults subgroup; Tebbe 2010 [184] – heart failure subgroup)	Intervention (n=1626): LMWH, certoparin 3,000 U anti Xa OD(standard dose), subcutaneously given, once daily. People within the certoparin treatment group also received two placebo injections. The intervention was given at regular intervals of 8 hours for 8-20 days.	n=3244 Older people hospitalised with acute medical condition and who have a significant decrease in mobility (bedridden or only able to walk short distances) expected for at least 4 days. Reasons for	All-cause mortality (90 days): definition not reported PE (90 days): confirmed by compression ultrasound sonography Major bleeding (time-point not reported): fatal bleeding, clinically overt bleeding associated with a fall of the haemoglobin concentration greater	New study

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Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=1618): 5000 IU UFH t.i.d., subcutaneously given, three times daily. The intervention was given at regular intervals of 8 hours for 8-20 days.	hospitalisation: Infections and infestations 27.6%, cardiac disorders 22.2%, respiratory, thoracic and mediastinal disorders 17.3%, nervous system disorders 6.6%, gastrointestinal disorders 6.6%, vascular disorders 5.8% Age: >70 years; mean ±SD 79.0±6.1 years Gender (male to female ratio): 1.56:1 Germany	than 2 g/l compared to the baseline haemoglobin concentration, clinically overt bleeding that required transfusion of two or more units of packed red cells or whole blood, symptomatic bleeding in a critical area or organ (intracranial, intraspinal, retroperitoneal and pericardial). Heparin-induced thrombocytopenia (time-point not reported)	
Samama 1999 [169]	Intervention 1 (n=364): LMWH, enoxaparin 20 mg (low dose), subcutaneously given once daily. 20 mg of enoxaparin in 0.2 ml of water for injectable preparations. Start time: within 24 hours after randomisation Treatment scheduled to last 6-14 days Intervention 2 (n=367): LMWH, enoxaparin 40 mg (standard dose), subcutaneously given once daily. 40 mg of enoxaparin in 0.2 ml of water for injectable preparations. Start time: within 24 hours after randomisation Treatment scheduled to last 6-14 days Comparison (n=371): Placebo (0.2 ml of	n=1102 People hospitalised with acute medical condition Reasons for hospitalisation: NYHA class III chronic heart failure (CHF), NYHA class IV CHF, acute respiratory failure, acute infectious disease , acute rheumatic disorder, inflammatory bowel disease (number of people with each condition not clearly reported) Age (mean): 73.5 years Gender (male to female ratio): 1:1 International: 60 centres in 9 countries (no further details about countries involved in the study)	All-cause mortality (1-110 days) Fatal PE (1-110 days): confirmed by autopsy PE (symptomatic) (1-110 days): confirmed by high-probability lung scanning, pulmonary angiography, or helical computed tomography or at autopsy DVT (symptomatic and asymptomatic) (1-110 days): confirmed by systematic ascending contract venography of the legs between days 6 and 14, or earlier if thrombosis was clinically suspected. If venography was infeasible venous ultrasonography was performed. Major bleeding (days 1-14): definition not reported	Included in CG92

Study	Intervention and comparison	Population	Outcomes	Comments
	isotonic water) Start time: within 24 hours after randomisation Treatment scheduled to last 6-14 days in the hospital <u>Concomitant treatment:</u> Elastic bandages or support stockings, and physiotherapy were used according to the usual practice at each centre (proportion of people within the study that used the stockings not reported)			
Schellong 2010 [173]	<u>Intervention (n=163):</u> LWMH, certoparin 3000 IU (standard dose), single daily dose during the treatment period Duration: 10±2 days <u>Comparison (n=174):</u> UFH, 7500 IU twice daily given subcutaneously during the treatment period Duration: 10±2 days	n=337 People hospitalised with acute medical condition and who have a significant recent decrease in mobility (completely bedridden or only able to walk short distances with the support of a nurse) Age: >40 years; mean±SD 70.6 ±12.3 years Gender (male to female ratio): Not reported Germany	All-cause mortality (90 days) DVT (symptomatic and asymptomatic) (90 days): assessed with the use of complete compression ultrasound (CCUS) of the lower extremity veins. PE (symptomatic and asymptomatic) (90 days: definition not reported Heparin-induced thrombocytopenia (90 days)	New study

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Table 88: Clinical evidence summary: LMWH (standard dose; standard duration) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (95% CI)
All-cause mortality	6938 (4 studies) not reported- 110 days	LOW[a,b] due to risk of bias, indirectness	RR 0.97 (0.83 to 1.13)	85 per 1000	3 fewer per 1000 (from 14 fewer to 11 more)
DVT (symptomatic and asymptomatic)	535 (1 study) not reported - 110 days	LOW[a,b] due to risk of bias, indirectness	RR 0.39 (0.23 to 0.67)	160 per 1000	97 fewer per 1000 (from 53 fewer to 123 fewer)
PE (symptomatic or asymptomatic)	4013 (3 studies) not reported - 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.6 (0.25 to 1.45)	7 per 1000	3 fewer per 1000 (from 5 fewer to 3 more)
Major bleeding	4051 (3 studies) not reported	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.53 (0.8 to 2.92)	7 per 1000	4 more per 1000 (from 1 fewer to 13 more)
PE, fatal	4294 (3 studies) not reported - 90 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.58 (0.31 to 1.11)	9 per 1000	4 fewer per 1000 (from 6 fewer to 1 more)
Heparin-induced thrombocytopenia	280 (1 study) not reported	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.33 (0.04 to 3.17)	21 per 1000	14 fewer per 1000 (from 21 fewer to 46 more)
Clinically relevant non-major bleeding	8307 (1 study) 8 days	VERY LOW[a,c] due to risk of bias, imprecision	RR 1.27 (0.63 to 2.56)	3 per 1000	1 more per 1000 (from 1 fewer to 5 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (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 outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 89: 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	270 (1 study) 10 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.00 (0.33 to 3.02)	44 per 1000	0 fewer per 1000 (from 30 fewer to 90 more)
DVT (symptomatic and asymptomatic)	263 (1 study) 10 days	LOW[a,b] due to risk of bias, imprecision	RR 0.33 (0.11 to 1.00)	92 per 1000	61 fewer per 1000 (from 82 fewer to 0 more)
PE, fatal	263 (1 study) 10 days	VERY LOW[b] due to risk of bias, imprecision	RR 0.33 (0.03 to 3.14)	23 per 1000	15 fewer per 1000 (from 22 fewer to 49 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 90: Clinical evidence summary: LMWH (low dose; standard duration) versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (low) (95% CI)
All-cause mortality	713	VERY LOW[a,b,c]	RR 1.05	138 per 1000	7 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with LMWH (low) (95% CI)
	(1 study) 110 days	due to risk of bias, indirectness, imprecision	(0.73 to 1.51)		(from 37 fewer to 70 more)
DVT (symptomatic and asymptomatic)	526 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.05 (0.71 to 1.54)	160 per 1000	8 more per 1000 (from 46 fewer to 86 more)
PE	526 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.33 (0.03 to 3.18)	11 per 1000	8 fewer per 1000 (from 46 fewer to 86 more)
Major bleeding	713 (1 study) 14 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.59 (0.17 to 2)	19 per 1000	8 fewer per 1000 (from 16 fewer to 19 more)
PE, fatal	526 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 1.00 (0.06 to 16.03)	4 per 1000	0 fewer per 1000 (from 4 fewer to 54 more)

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

Table 91: Clinical evidence summary: LMWH (high 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 LMWH (standard dose)	Risk difference with LMWH (high dose) (95% CI)
All-cause mortality	91 (1 study) 14 days	LOW[a] due to imprecision	Peto OR 0.13 (0 to 6.67)	22 per 1000	19 fewer per 1000 (from 22 fewer to 109 more)
Major bleeding	91 (1 study)	LOW[a] due to imprecision	Not estimable[b]	Not estimable[b]	0 fewer per 1000 (from 40 fewer to 40 more)[b]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (standard dose)	Risk difference with LMWH (high dose) (95% CI)
	14 days				
Heparin-induced thrombocytopenia	91 (1 study) 14 days	LOW[a] due to imprecision	Not estimable[b]	Not estimable[b]	0 fewer per 1000 (from 40 fewer to 40 more)[b]

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

Table 92: Clinical evidence summary: LMWH (standard dose; standard duration) versus LMWH (low dose; standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (low dose)	Risk difference with LMWH (standard dose) (95% CI)
All-cause mortality	711 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.78 (0.53 to 1.15)	145 per 1000	32 fewer per 1000 (from 68 fewer to 22 more)
DVT (symptomatic and asymptomatic)	535 (1 study) 110 days	LOW[a,b] due to risk of bias, indirectness	RR 0.37 (0.22 to 0.64)	167 per 1000	105 fewer per 1000 (from 60 fewer to 130 fewer)
PE	535 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.13 (0.00 to 6.59)	4 per 1000	3 fewer per 1000 (from 4 fewer to 21 more)
Major bleeding	711 (1 study) 14 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 5.85 (0.71 to 48.34)	3 per 1000	14 more per 1000 (from 1 fewer to 135 more)
PE, fatal	535 (1 study) 110 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 1.89 (0.20 to 18.23)	4 per 1000	3 more per 1000 (from 3 fewer to 61 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (low dose)	Risk difference with LMWH (standard dose) (95% CI)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.					

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH (standard duration)	Risk difference with LMWH (extended duration) (95% CI)
All-cause mortality	4335 (1 study) 90 days	LOW[a,b] due to risk of bias, imprecision	RR 1.01 (0.77 to 1.31)	48 per 1000	0 more per 1000 (from 11 fewer to 15 more)
PE	3685 (1 study) 90 days	VERY LOW[b] due to risk of bias, imprecision	RR 0.44 (0.11 to 1.7)	4 per 1000	2 fewer per 1000 (from 3 fewer to 3 more)
PE, fatal	3685 (1 study) 90 days	VERY LOW[b] due to risk of bias, imprecision	Peto OR 0.14 (0.11 to 1.7)	1 per 1000	1 fewer per 1000 (from 1 fewer to 1 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 94: Clinical evidence summary: LMWH (standard dose; standard duration) + AES versus AES

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES	Risk difference with LMWH + AES (95% CI)
All-cause mortality	8307 (1 study) 90 days	HIGH	RR 0.97 (0.84 to 1.12)	86 per 1000	3 fewer per 1000 (from 14 fewer to 10 more)
Major bleeding	8307 (1 study) 8 days	LOW[a] due to imprecision	RR 1.44 (0.67 to 3.10)	3 per 1000	1 more per 1000 (from 1 fewer to 6 more)
Clinically relevant non-major bleeding	8307 (1 study) 8 days	LOW[a] due to imprecision	RR 1.27 (0.63 to 2.56)	3 per 1000	1 more per 1000 (from 1 fewer to 5 more)

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

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH	Risk difference with LMWH (95% CI)
All-cause mortality	6496 (5 studies) 8 - 90 days	VERY LOW[a,b,d] due to risk of bias, inconsistency, imprecision	RR 0.93 (0.59 to 1.45)	37 per 1000	3 fewer per 1000 (from 15 fewer to 17 more)
DVT (symptomatic and asymptomatic)	1539 (3 studies) 8 - 90 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 0.57 (0.37 to 0.87)	65 per 1000	28 fewer per 1000 (from 8 fewer to 41 fewer)
PE	6066 (5 studies) 8 - 90 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 0.73 (0.31 to 1.73)	4 per 1000	1 fewer per 1000 (from 3 fewer to 3 more)
Major bleeding	6545 (5 studies) 8 - 90 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 0.64 (0.33 to 1.23)	8 per 1000	3 fewer per 1000 (from 5 fewer to 2 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with UFH	Risk difference with LMWH (95% CI)
PE, fatal	2041 (2 studies) not reported	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	Peto OR 0.92 (0.06 to 14.82)	1 per 1000	0 fewer per 1000 (from 1 fewer to 14 more)
Heparin-induced thrombocytopenia	3666 (2 studies) 90 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	Peto OR 0.31 (0.05 to 1.79)	2 per 1000	2 fewer per 1000 (from 2 fewer to 2 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Apixaban	Risk difference with LMWH (95% CI)
All-cause mortality	6528 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.49 (0.25 to 8.92)	1 per 1000	0 more per 1000 (from 0 fewer to 5 more)
PE	6517 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.14 (0.41 to 3.13)	2 per 1000	0 more per 1000 (from 1 fewer to 5 more)
Major bleeding (including fatal bleeding)	6401 (1 study) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.4 (0.15 to 1.02)	5 per 1000	3 fewer per 1000 (from 4 fewer to 0 more)
Major plus clinically relevant non-major bleeding	6401 (1 study)	LOW[a,b] due to risk of bias,	RR 0.78 (0.57 to	27 per 1000	6 fewer per 1000 (from 11 fewer to 2 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Apixaban	Risk difference with LMWH (95% CI)
	30 days	imprecision	1.07)		

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 97: Clinical evidence summary: Rivaroxaban versus LMWH (standard dose; standard duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH	Risk difference with Rivaroxaban (95% CI)
All-cause mortality	6265 (1 study) 35 days	MODERATE[a] due to imprecision	RR 1.06 (0.86 to 1.32)	48 per 1000	3 more per 1000 (from 7 fewer to 15 more)
DVT (symptomatic and asymptomatic)	6024 (1 study) 35 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.81 (0.64 to 1.02)	48 per 1000	9 fewer per 1000 (from 17 fewer to 1 more)
PE	6024 (1 study) 35 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.74 (0.33 to 1.65)	5 per 1000	1 fewer per 1000 (from 3 fewer to 3 more)
Major bleeding	7998 (1 study) 35 days	HIGH	RR 3.07 (1.68 to 5.61)	3 per 1000	7 more per 1000 (from 2 more to 16 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
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 98: Clinical evidence summary: Fondaparinux versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with Fondaparinux (95% CI)
All-cause mortality	839 (1 study) 30 days	LOW[a,b] due to risk of bias, imprecision	RR 0.55 (0.29 to 1.03)	60 per 1000	27 fewer per 1000 (from 43 fewer to 2 more)
DVT (symptomatic and asymptomatic)	644 (1 study) 15 days	LOW[a,b] due to risk of bias, imprecision	RR 0.62 (0.35 to 1.1)	90 per 1000	34 fewer per 1000 (from 58 fewer to 9 more)
PE	839 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.24 (0.03 to 2.17)	10 per 1000	7 fewer per 1000 (from 9 fewer to 11 more)
Major bleeding	839 (1 study) 15 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.97 (0.06 to 15.60)	2 per 1000	0 fewer per 1000 (from 2 fewer to 34 more)
PE, fatal	839 (1 study) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.42 (0.11 to 1.6)	17 per 1000	10 fewer per 1000 (from 15 fewer to 10 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.

16.4 Economic evidence

Published literature

An original model was developed in CG92 for this question and is included here.[124] Additionally, two health economic studies were identified with the relevant comparison and have been included in this review. [115,199] These are summarised in the health economic evidence profiles below (Table 99, Table 100 and Table 101) and the health economic evidence tables in appendix J.

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

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Table 99: Health economic evidence profile: LMWH (standard dose, standard duration), UFH (standard duration), Fondaparinux (standard duration) vs no prophylaxis

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
National Guideline Centre 2010[124] ([UK])	Directly applicable [(a)]	Potentially serious limitations [(b)]	**-Study design:** CUA using decision analytic model based on NMAs **-Population:** Adult (18 years or older) admitted as general medical admissions to hospitals in England. **-Interventions:** **1.** No prophylaxis **2.** LMWH (average of dalteparin 5000 units subcutaneously daily) and enoxaparin (4000 units subcutaneously daily) **3.** UFH (5000 units three times daily) **4.** Fondaparinux sodium (2.5 mg subcutaneously daily)	NR	NR	**Incremental net monetary benefit (INMB):** No prophylaxis: £0 LMWH: £328 UFH: £118 Fondaparinux: -£61	None of the sensitivity analyses undertaken changed the most cost-effective strategy except where the baseline risk of PE is very low and that of MB is increased, where the strategy of no prophylaxis becomes the most cost-effective strategy.

Abbreviations: CUA: cost-utility analysis; DVT: deep vein thrombosis; ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; 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.

(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 NMA.

Table 100: Health economic evidence profile: LMWH (standard dose, standard duration) vs no prophylaxis

Study	Applicability	Limitations	Other comments	Cost	Effects	Incremental costs	Incremental effects	Cost effectiveness	Uncertainty
Millar 2016 [115] ([Australia])	Partially applicable[(a)]	Potentially serious limitations [(b)]	**-Study design:** Cost-consequences analysis using decision tree model based on the results of a single RCT (the PREVENT trial) **-Population**: adult internal medicine patients admitted to all Australian hospitals **-Interventions:** 1. No prophylaxis 2. VTE prophylaxis using LMWH (Enoxaparin 40 mg/day). Three levels of eligibility for prophylaxis were examined: 2.a. restricted[(d)] (25% of all admissions), 2.b. intermediate[(c)] (40% of all admissions) and 2.c. broad[(e)] (80% of all admissions)	1. £29	1. 4.3 DVTs, 2.3 PEs, 0.4 deaths per 1000	DVT: No prophylaxis: dominated Restricted eligibility: baseline Intermediate eligibility: extendedly dominated Broad eligibility: £29,861 per DVT averted			A range of sensitivity analyses were conducted including changing baseline VTE risk, fatality rate for PE and major bleeding and assumptions regarding VTE risk in non-eligible patients.
				2.a. £26	2.a. 2.5 DVTs, 2 PEs, 0.5 deaths per 1000	PE: No prophylaxis: dominated Restricted eligibility: baseline Intermediate eligibility: extendedly dominated Broad eligibility: £170,827 per DVT averted			
				2.b. £30	2.b. 2.4 DVTs, 1.99 PE, 0.6 deaths	Deaths: No prophylaxis: £30,000 per death averted Restricted eligibility: baseline Intermediate eligibility: dominated Broad eligibility: dominated			
				2.c. £39	2.c. 2.1 DVTs, 1.93 PEs, 0.9 deaths per 1000				

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

(a) Some uncertainty regarding the applicability of resource use and cost data from Australia in 2014 to current NHS context. Discounting was used only for health outcomes and the rate used is different from that recommended in the NICE Reference Case. QALYs are not used as an outcome measure.

(b) The model has a short time horizon that covers only the duration of the hospital stay, hence, does not capture long term costs. Only symptomatic events are included in the model. The source of baseline risk and relative treatment effects is based on a single trial and is not reflective of the total body of evidence. The results of the costs and outcomes are not presented as means per patient.

(c) Restricted: where only patients with strongest risk factors were given prophylaxis (malignancy, especially with chemotherapy, previous history of VTE, some rarer high risk conditions such as inflammatory bowel disease. (~ 25% of all inpatient admissions)

(d) Intermediate: where patients with strong and moderate risk factors, such as cardiac or respiratory failure, sepsis or inflammation, are given prophylaxis (~ 40% of all inpatient admissions)

(e) Broad: where everyone from the intermediate group as well as those satisfying an age criterion (>40 or >60) are given prophylaxis (~80% of all inpatient admissions)

Table 101: Health economic evidence profile: LMWH (standard dose, standard duration) vs UFH (standard duration)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Wilbur 2011[199] ([Canada])	Partially applicable[(a)]	Potentially serious limitations[(b)]	**-Study design:** Cost-consequences analysis using decision tree model **-Population**: Hypothetical cohort of adult internal medicine patients. Results were reported separately for the cancer subgroup **-Interventions:** 1. UFH (5000 U, twice daily [bid], SC]) initiated on day 1 of hospital stay and continued for 7 days 2. LMWH (enoxaparin 40 mg, once daily [od], administered subcutaneously [SC]) initiated on day 1 of hospital stay and continued for 7 days	**2 vs 1:** £4 **Cancer subgroup** 2 vs 1: £2	**2 vs 1:** 3 **less** True DVT events per 1000 1.3 **less** untoward events (PE, major bleeding and death) per 1000 **Cancer subgroup:** 2 vs 1: 6 **less** True DVT events per 1000 7 **less** untoward events (PE, major bleeding	**ICER:** £1,116 per DVT averted £3,726 per untoward event averted **Cancer subgroup:** ICER: £287 per DVT averted £1,037 per untoward event averted	Wide range of one-way sensitivity analyses was conducted. Overall, the results were consistent across the different scenarios considered.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
					and death) per 1000		

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

(a) Some uncertainty regarding the applicability of resource use and cost data from Canada in 2009 to current NHS context. The perspective used was that of the institution. QALYs are not used as an outcome measure.

(b) The model has a short time horizon that covers only the duration of the hospital stay (7 days), hence, does not capture long term costs and effects. The main outcome reported (untoward events) is a composite outcome measure and its use would underestimate the rate of these events as the occurrence of multiple events is counted as one event. The source of baseline risk and relative treatment effects is slightly outdated. Unit costs are based on both national and local sources and it is not clear if the local sources are reflective of national unit costs. The results of the sensitivity analysis were not reported for the cancer subgroup.

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16.5 Evidence statements

Clinical

LMWH at a standard dose for a standard duration was compared with no prophylaxis, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE, heparin-induced thrombocytopenia and clinically relevant non-major bleeding were reported across four studies. There was clinical benefit of LMWH in terms of all-cause mortality and DVT (symptomatic and asymptomatic), although the mortality outcome was also consistent with no difference. There was possible clinical benefit in terms of PE, fatal PE and heparin-induced thrombocytopenia, although there was considerable uncertainty around these results. There was possible clinical harm in terms of major bleeding and clinically relevant non-major bleeding, however there was also considerable uncertainty around these results. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

LMWH at a high dose for a standard duration was compared with no prophylaxis, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic) and fatal PE were reported in one study. There was possible clinical benefit of LMWH in terms of DVT (symptomatic and asymptomatic) and fatal PE and no clinical difference in terms of all-cause mortality, however the considerable uncertainty around these results meant that they could in fact be consistent with harm, no difference and benefit. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

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

LMWH at a high dose for a standard duration was compared with LMWH at a standard dose at a standard duration, the outcomes all-cause mortality, major bleeding and heparin-induced thrombocytopenia were reported in one study. There was possible clinical benefit of LMWH in terms of all-cause mortality and no clinical difference in terms of major bleeding and heparin-induced thrombocytopenia. However there was considerable uncertainty around all these results. The quality of the evidence was low due to imprecision.

LMWH at a standard dose for a standard duration was compared with LMWH at a low dose at a standard duration, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and fatal PE were reported in one study. Low quality evidence showed clinical benefit of LMWH at a standard dose for DVT (symptomatic and asymptomatic). Very low quality evidence suggested possible clinical benefit of LMWH at a standard dose in terms of all-cause mortality and PE. There was possible clinical harm of LMWH at a standard dose in terms of major bleeding and fatal PE. However for these four outcomes there was considerable uncertainty around the results. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision.

LMWH at a standard dose for an extended duration was compared with LMWH at a standard dose for a standard duration, the outcomes all-cause mortality, PE and fatal PE were reported in one

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study. There was possible clinical benefit of LMWH for an extended duration in terms of PE and fatal PE, but these results were also consistent with both no difference and possible harm when considering their uncertainty. There was no clinical difference in terms of all-cause mortality. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

LMWH at a standard dose for a standard duration in combination with AES was compared with AES alone, the outcomes all-cause mortality, major bleeding and clinically relevant non-major bleeding were reported in one study. There was a suggested clinical benefit of LMWH in combination with AES in terms of all-cause mortality, however this finding was also consistent with no difference. There was possible clinical harm of LMWH in combination with AES in terms of major bleeding and clinically relevant non-major bleeding, however there was very serious imprecision around both of these results. The quality of the evidence ranged from low to high due to imprecision. The outcome with high quality evidence was all-cause mortality.

LMWH at a standard dose for a standard duration was compared with UFH, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding, fatal PE and heparin-induced thrombocytopenia were reported across five studies. There was possible clinical benefit of LMWH in terms of all-cause mortality, DVT (symptomatic and asymptomatic), major bleeding, heparin-induced thrombocytopenia. However the uncertainty around these results was also consistent with no difference and in some cases clinical harm (all cause mortality and HIT). There was no clinical difference in terms of PE and fatal PE, however there was also uncertainty around these results. The quality of the evidence was very low due to risk of bias, indirectness, imprecision and inconsistency.

LMWH at a standard dose for a standard duration was compared with apixaban, the outcomes all-cause mortality, PE and major bleeding were reported in one study. There was possible clinical benefit of LMWH in terms of major bleeding, however the imprecision around this result may also have been consistent with no difference. There was no clinical difference in terms of all-cause mortality and PE, but the imprecision around these results showed consistency with both possible benefit and harm. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

Rivaroxaban was compared with LMWH at a standard dose for a standard duration, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE and major bleeding were reported in one study. There was possible clinical benefit of rivaroxaban in terms of PE, however the uncertainty around this result was also consistent with no difference or harm. High quality evidence showed clinical harm of rivaroxaban in terms of major bleeding, Moderate quality evidence suggested possible clinical harm in terms of all-cause mortality, although this finding was also consistent with no difference. There was no clinical difference in terms of DVT (symptomatic and asymptomatic). The quality of the evidence ranged from very low to high due to risk of bias, indirectness and imprecision. The outcome with high quality evidence was major bleeding.

Fondaparinux was compared with no prophylaxis, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and fatal PE were reported in one study. There was possible clinical benefit of fondaparinux in terms of all-cause mortality, DVT (symptomatic and asymptomatic), PE and fatal PE, however the uncertainty around these results were also consistent with no difference and in the case of the PE outcomes, also clinical harm. There was no clinical difference in terms of major bleeding, although this finding was also very uncertain. The quality of the evidence ranged from very low to low due to risk of bias and imprecision.

Economic

- One cost-utility analysis found that for VTE prophylaxis in general medical patients admitted to hospital the following interventions were cost-effective (having positive incremental net monetary benefit [INMB) compared to no prophylaxis: low molecular weight heparin (standard

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dose, standard duration) (INMB: 328), unfractionated heparin (standard duration)(INMB: £118). The same analysis found that for VTE prophylaxis in general medical patients admitted to hospital fondaparinux sodium (standard duration) was not cost-effective compared to no prophylaxis (INMB: -£61). This analysis was assessed as directly applicable with potentially serious limitations.

- One cost-consequences analysis found that in general medical patients admitted to hospital:
  - Restricted eligibility to VTE prophylaxis (25% of all admissions) is less costly (£3 less per patient) and had 0.0018 fewer DVT events per patient and 0.0003 fewer PE events per patient but 0.0001 more deaths per patient compared to no prophylaxis.
  - Intermediate eligibility to VTE prophylaxis (40% of all admissions) is more costly (£1 more per patient) and had 0.0019 fewer DVT events per patient and 0.0003 fewer PE events per patient but 0.0002 more deaths per patient compared to no prophylaxis.
  - Broad eligibility to VTE prophylaxis (80% of all admissions) is more costly (£10 more per patient) and had 0.0022 fewer DVT events per patient and 0.0004 fewer PE events per patient but 0.0005 more deaths per patient compared to no prophylaxis.

  This analysis was assessed as partially applicable with potentially serious limitations.

- One cost-consequences analysis found that for VTE prophylaxis:
  - In internal medicine patients admitted to hospital, low molecular weight heparin (standard dose, standard duration) was more costly (£4 more) and had 0.003 fewer DVT events per patient and 0.013 fewer untoward events (PE, major bleeding and death) per patient compared to unfractionated heparin (standard duration).
  - In the cancer patients sub group, low molecular weight heparin (standard dose, standard duration) was more costly (£2 more per patient) and had 0.006 fewer DVT events per patient and 0.007 fewer untoward events (PE, major bleeding and death) per patient compared to unfractionated heparin (standard duration).

This analysis was assessed as partially applicable with potentially serious limitations.

16.6 Recommendations and link to evidence

Recommendations	**1.4.6 Offer pharmacological VTE prophylaxis for a minimum of 7 days to acutely ill medical patients whose risk of VTE outweighs their risk of bleeding:** • **Use low-molecular-weight heparin (LMWH)[qqq] as first-line treatment.** • **If LMWH[rrr] is contraindicated use fondaparinux sodium[sss]. [2018]** **1.4.7 If using pharmacological VTE prophylaxis for people with renal impairment choose either LMWH[ttt] or unfractionated heparin (UFH).**

[qqq] 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.

[rrr] 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.

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

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	[2018] **1.4.8 If needed, reduce the dose of LMWH[uuu] and UFH for people with renal impairment. Base the decision on multidisciplinary or senior opinion, or locally agreed protocols. [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 7–90 days from hospital discharge), pulmonary embolism (up to 7–90 days from hospital discharge), fatal PE (7–90 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 thrombocytopenia (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	Nineteen randomised controlled studies were included in this review. Nine of these studies were included in the previous guideline (CG92). Ten new studies were added to the review. Data from subgroup analyses following two of the included studies was included in the clinical evidence tables for information and was not analysed. One of the studies included had subgroup analyses evaluating people with cancer and health failure within the study population as well as the influence of age. The other study evaluated people with ischaemic stroke within the study population. Eleven comparisons were included in this review, evaluating the use of pharmacological (LMWH, UFH, apixaban, rivaroxaban and fondaparinux) and mechanical (AES) interventions for VTE prophylaxis. A majority of the studies evaluated the use of LMWH versus other pharmacological interventions. The committee noted that a number of studies failed to clearly define their outcomes or methods of ascertaining VTE events. This was particularly notable for the major bleeding outcome where many failed to clearly define this. The committee chose to include these papers and downgrade the evidence for indirectness of outcome. The committee noted that overall the quality of evidence was low due to an increased risk of bias across many studies and imprecision around the effect estimates.
Trade-off between	Overall, the committee considered that the clinically beneficial effects of LMWH and

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clinical benefits and harms	fondaparinux were prominent enough to adopt the recommendation from CG92. The committee commented that the LMWHs that are more commonly used in practice in the acutely ill medical population are enoxaparin, dalteparin and tinzaparin. The committee also noted that a majority of the studies evaluated patients who are at higher risk of VTE, including older adults and people who are immobilised. The committee noted that DOACs offered equal benefit in reduction of VTE compared to LMWH, however they also led to an increased risk of major bleeding. The committee also noted that DOACs are not currently licenced for use in acutely ill medical patients. NICE policy states that off‑label use may be recommended if the clinical need cannot be met by a licensed product and there is sufficient evidence and/or experience of using the medicine to demonstrate its safety and efficacy to support this. As clinical need can be met by a licensed product (i.e. LMWH), DOACs were not recommended. The committee wished to highlight that there was no evidence for the effectiveness of mechanical prophylaxis in this population. Therefore given the size of this population and possible resource impact of recommending AES or IPCD which have no proven benefit, the committee decided not to make a recommendation about mechanical prophylaxis. For those contraindicated for pharmacological prophylaxis, the committee decided that the clinician must use clinical judgement to weigh the risk of VTE with the risk of bleeding, and for those with a high risk of bleeding or for those who may be contraindicated for pharmacological prophylaxis for other reasons, they did not feel they could recommend mechanical prophylaxis on the basis of no evidence.
Trade-off between net clinical effects and costs	Three economic studies were included for this review. One was the model from CG92 which compared LMWH (standard dose, standard duration), UFH (standard duration), fondaparinux (standard duration) to no prophylaxis. The second compared LMWH (standard dose, standard duration) to no prophylaxis and the third compared LMWH (standard dose, standard duration) to UFH (standard duration). The CG92 model was assessed as directly applicable while the other two studies were assessed as partially applicable. All three studies were assessed to have potentially serious limitations. The committee noted that there was potential for the DOACs to offer an advantage in this population given their effectiveness in relation to DVT and PE compared to LMWH (standard dose, standard duration), and their oral route of administration and lower acquisition cost; however; it was noted that they also had a much higher risk of bleeding, so it is not clear whether they would be cost-effective in this population. The committee noted that without a clear evidence of benefit, these DOACs would not be recommended for off-label use in this population. The committee discussed the evidence and noted the lack of good quality evidence to support the use of mechanical prophylaxis in this population despite its potential benefit from reducing the use of pharmacological prophylaxis, with its associated risk of bleeding, in this largely elderly and immobile population. The committee determined that the new evidence is in line with current practice (that largely followed the CG92 recommendation), to offer pharmacological prophylaxis for people assessed to be at higher risk of VTE and low risk of bleeding. Hence, the committee decided to adopt the CG92 recommendation. The committee discussed whether both LMWH and fondaparinux should be offered as options, given that fondaparinux was not cost-effective according to CG92 model, and decided that fondaparinux can be recommended only as an option if LMWH was contraindicated.
Other considerations	The committee commented on the broad terminology used in the previous guideline for this population – general medical patients. It is difficult to define this population as definitions can vary across hospital settings. The committee considered a more helpful term would be acutely ill medical patients (for example acute medical

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	admissions), but appreciated the fact that no matter what terminology is used this population is very mixed, presenting patients with different risks of developing VTE. The committee discussed that there is a high prescription rate of pharmacological VTE prophylaxis within this population and thus discussed the crucial need for an appropriate risk tool that will effectively reduce the number of patients being given VTE prophylaxis when they are not highly at risk of VTE. The committee agreed it necessary to highlight the particular need for VTE risk assessment in this population to ensure that VTE prophylaxis is not over-prescribed. The committee discussed the use of VTE prophylaxis in people with renal impairment (eGFR <30 ml/min). Based on the pharmacokinetics, manufacturer's licensing and known clinical practice, the committee determined that LMWH or unfractionated heparin would be the most appropriate options for prophylaxis in this population, rather than fondaparinux or oral anticoagulants because the risk of bleeding may be increased in the renal impairment population. Because of this, dose reduction of LMWH or UFH may be required. Unfractionated heparin may occasionally be preferred to LMWH as it has a shorter half life and it can be reversed with protamine. Additionally it does not usually require dose adjustment in patients with significant renal impairment . It may be preferred in patients where reversal may be required, for example if bleeding may occur or there may be a need for acute surgery. The two recommendations for people with renal impairment will be cross-referred to from each of the different population chapters within the guideline.

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