National Institute for Health and Care Excellence

Draft

Venous thromboembolism in over 16s

Reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism

NICE guideline

Appendices J – U

October 2017

Draft for consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

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Appendices

Appendix J: Health economic evidence tables

J.1 Risk assessment for medical, surgical and trauma patients

J.1.1 Accuracy of risk assessment tools for VTE in hospital admissions

No relevant economic evaluations were identified.

J.1.2 Accuracy of risk assessment tools for bleeding in hospital admissions

No relevant economic evaluations were identified.

J.1.3 Effectiveness of risk assessment tools in hospital admissions

Study	[Lecumberri 2011[546]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CCA (health outcome: objectively confirmed VTE events during hospitalisation, major bleeding, surgical re-operation, mortality (not reported in the paper) **Study design:** before and after comparison **Approach to analysis:** Analysis of patient level data on costs and incidence of VTE	**Population:** All hospitalised adult inpatients (medical and surgical) at the University Clinic of Navarra. The population also included pregnant women but very small percentage ranging between 3.2 to 4.4% across the follow-up periods. **Cohort settings:** **Mean age**: Intervention 1: 55 years Intervention 2: 55 years **Male**: Intervention 1 (January to June	**Total costs (mean per patient):** Intervention 1: £28 Intervention 2: £22 Incremental (2−1): -£6 (95% CI: NR; p=NR) **Currency & cost year:** 2009 Euros [(presented here as 2009 UK pounds[(b)])] **Cost components incorporated:** Tests for diagnosing	**VTE (events per patient):** Intervention 1: 0.003 events Intervention 2: 0.001 to 0.002 events Incremental (2−1): -0.002 to –0.001 events (95% CI: NR; p=NR) **Major bleeding (events per patient)** Intervention 1: 0.09 events Intervention 2: 0.08 to 0.077 events Incremental (2−1): - 0.01 events	**ICER (Intervention 2 versus Intervention 1):** Dominant 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): n/a **Analysis of uncertainty:** One way sensitivity analyses were conducted, varying the estimates about clinical effectiveness with the bounds of their 95% CI. Worst and best case scenarios were determined by considering the

Perspective: Spanish institutional perspective **Follow-up:** 6 months before and four 6-months periods over 4 consecutive years after the implementation of the e-alert system. **Treatment effect duration:**[(a)] length of hospitalisation **Discounting:** Costs: n/a ; Outcomes: n/a	2005): 55% Intervention 2: Period 1 (January to June 2006): 54% Period 2 (January to June 20067: 53% Period 3 (January to June 2008): 53% Period 4 (January to June 2009): 53% **Intervention 1: (n=6,441)** No e-alert system to stratify patients' risk of thrombosis. **Intervention 2: (n=25,839 [>6000 per period], 47% medical patients and 53% surgical patients)** E-alert software to identify hospitalised patients at risk of VTE, linked to the computerised patients' database to use data on patient characteristics to stratify patients' thrombotic risk. Risk stratification was carried out using: - PRETEMED scale (a validated risk stratification tool) for medical patients. This is a point scale with major VTE risk factors (e.g. active cancer, previous VTE, acute MI, ischaemic stroke with limb paralysis, decompensated chronic obstructive pulmonary disease, and thrombophilia) were assigned a score of 3, congestive heart failure, chronic renal insufficiency/nephrotic syndrome, severe acute infection, lower limb cast or prolonged bed	suspected cases of VTE Treatment cost Follow-up visits Management of complications Software design and maintenance	(95% CI: NR; p=NR)	upper and lower cost estimates (real cost +/- 25%) and the lower and upper estimates of effectiveness. None of the sensitivity analyses resulted in a change of the conclusion regarding dominance of the intervention.

	rest were assigned a score of 2, pregnancy/post-partum period, recent prolonged flight, lower limb paresis, oestrogen therapy, thalidomide/lenalidomide administration, use of central vein catheter, obesity, age>60 years or smoking assigned a score of 1. High risk of VTE was defined as cumulative risk score of at least 4 points. - ACCP guidelines for surgical patients Screening was undertaken daily and alerts sent for those with high risk so that the physician can either order or withhold the prophylaxis. The prophylaxis guidelines were also displayed. Low molecular weight heparin (LMWH) was recommended for all high risk patients except those with high risk of bleeding where mechanical prophylaxis is recommended (elastic stockings or pneumatic compression devices)			

Data sources

Health outcomes: data on the incidence of VTE during hospitalisation were obtained from the hospital local databases (the Hospital Discharge Minimum Basic Dataset), which includes clinical and administrative data on each hospital discharge. **Cost sources:** costs were calculated according to the hospital local costs.

Comments

Source of funding: institutional funding. **Limitations:** The risk assessment tools used are different from those included in the clinical review. QALYs are not used as measure of outcome. Uncertainty regarding the applicability of costs and resource use from the Spanish health care system in 2011 to current NHS perspective. The economic analysis is conducted alongside a single observational study, so by definition does not reflect all evidence in this area. Short follow-up period, so long terms and consequences have not been included. Unit costs are based on local rather than national sources; hence it is not clear if these are generalisable.

Overall applicability:[c] partially applicable **Overall quality**[d] potentially serious limitations

Abbreviations: CCA: cost-consequence analysis; 95% CI: 95% confidence interval; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2009 purchasing power parities[715]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**[Millar 2016[640]]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CCA (health outcomes: deaths, non-fatal VTE events avoided) **Study design:** decision tree model **Approach to analysis:** a decision tree model was designed based on the results of the PREVENT trial. **Perspective:** Australian public health care system **Follow-up:** inpatient admission period	**Population:** Adult patients admitted to Australian hospital as medical inpatients. **Cohort settings:** Start age: 74 years Male: NR **Intervention 1:** No VTE prophylaxis. **Intervention 2:** VTE prophylaxis using LMWH (Enoxaparin 40 mg/day). Three levels of eligibility for prophylaxis	**Total cost[b] (mean per patient):** Intervention 1: £29 Intervention 2-Restricted : £26 Intervention 2-Intermediate : £30 Intervention 2-Broad : £39 **Currency & cost year:** Australian dollars presented here as 2014 UK pounds[c] **Cost components incorporated** LMWH prophylaxis Treatment costs for DVT, PE,	**Deaths[b] (mean per patient):** Intervention 1: 0.0004 Intervention 2: Restricted: 0.0005 Intermediate: 0.0006 Broad: 0.0009 **Total DVTs[b] (mean per patient):** Intervention 1: 0.0043 Intervention 2: Restricted: 0.0025 Intermediate: 0.0024 Broad: 0.0021	**ICER:** DVTs 1. No VTE Prophylaxis: dominated 2.a (Restricted eligibility): baseline 2.b. (Intermediate eligibility): extendedly dominated (da) 2.c. (Broad eligibility) vs 2.a. (restricted eligibility): £29,861 per DVT averted (da) **PEs** 1. No VTE Prophylaxis: dominated 2.a (Restricted eligibility): baseline 2.b. (Intermediate eligibility): extendedly dominated (da) 2.c. (Broad eligibility) vs 2.a. (restricted eligibility): £170,827 per DVT averted (da)

Treatment effect duration:[(a)] same as follow-up **Discounting:** Costs: n/a ; Outcomes: 3%	were examined: 2.a. 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) 2.b. 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) 2.c. 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)	PTS and major bleeds Nursing time Hospital costs GP visits Monitoring	**Total PEs[(b)] (mean per patient):** Intervention 1: 0.0023 Intervention 2: Restricted: 0.0020 Intermediate: 0.0020 Broad: 0.0019	**Death** 1. No VTE Prophylaxis: £30,000 per death averted 2.a (Restricted eligibility): baseline 2.b. (Intermediate eligibility): dominated (da) 2.c. (Broad eligibility) vs 2.a. (restricted eligibility): dominated (da) **Analysis of uncertainty:** 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.
Data sources				
Health outcomes: Data on symptomatic DVTs, PEs and major bleeding were based on the results of the PREVENT trial. **Quality-of-life weights:** n/a. **Cost sources:** national unit costs were used and these were obtained from the Medicare Benefits Schedule, Australia and the Department of Health and Ageing, Canberra.				

Comments
Source of funding: NR. **Limitations:** 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. 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.
Overall applicability:[b] Partially applicable **Overall quality**[c] Potentially serious limitations

Abbreviations: CEA: cost effectiveness and analysis; 95% CI: 95% confidence interval; da: deterministic analysis; DVT: Deep vein thrombosis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; n/a: not applicable; NR: not reported; pa: probabilistic analysis; PE: pulmonary embolism; QALYs: quality-adjusted life years; VTE: venous thromboembolism.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Calculated by NGC based on 1,458,600 inpatient admissions.

(c) Converted using 2014 purchasing power parity[715]

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

J.2 Risk assessment for people having day procedures

J.2.1 Accuracy of risk assessment tools for VTE for day procedures

No relevant economic evaluations were identified.

J.2.2 Accuracy of risk assessment tools for bleeding for day procedures

No relevant economic evaluations were identified.

J.2.3 Effectiveness of risk assessment tools for day procedures

No relevant economic evaluations were identified.

J.3 Reassessment of VTE and bleeding risk

J.3.1 Reassessment of risk for hospital admissions

No relevant economic evaluations were identified.

J.3.2 Reassessment of risk for day procedures

No relevant economic evaluations were identified.

J.4 Risk assessment for pregnant women and women up to 6 weeks postpartum

No relevant economic evaluations were identified.

J.5 Giving information to patients and planning for discharge

No relevant economic evaluations were identified.

J.6 General VTE prevention for everyone in hospital

No relevant economic evaluations were identified.

J.7 Nursing care: Early mobilisation and hydration

No relevant economic evaluations were identified.

J.8 Obesity

No relevant economic evaluations were identified.

J.9 People using antiplatelets

No relevant economic evaluations were identified.

J.10 People using anticoagulation therapy

No relevant economic evaluations were identified.

J.11 Acute coronary syndromes

No relevant economic evaluations were identified.

J.12 Acute stroke patients

Study	[CLOTS Trials Collaboration[184], Dennis 2015[248], Denis 2015[247]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: quality-adjusted life-days) **Study design:** Randomised Controlled Trial **Approach to analysis:** Within-trial analysis of individual patient level data of costs and outcomes using generalised linear modelling of cost data and **Perspective:** UK NHS **Follow-up:** 6 months	**Population:** Immobile stroke patients admitted to 92 UK centres from days 0 to 3 of admission. **Cohort settings: (n=2876)** Start age: 74.6 years Male: 48% **Intervention 1: (n=1438)** Usual care only. Routine care defined as early mobilisation hydration and anti-platelet or anti-coagulant medication.	**Total costs of IPC plus hospital days (mean per patient):** Intervention 1: £12,116 Intervention 2: £12,567 Incremental (2−1): £451 (95% CI: NR; p=NR) **Currency & cost year:** UK pounds [2013] **Cost components incorporated:** Hospital stay IPC cost (capital and equipment)	**Quality-adjusted life-days (mean per patient):** Intervention 1: 26.7 days Intervention 2: 27.6 days Incremental (2−1): 0.9 days (95% CI: -2.1 to +3.9; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £610.88 per quality adjusted life day (da) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Sensitivity analyses based on multiple imputations of the EQ5D-3L to account for missing data did not alter the conclusions. No other one way sensitivity analysis was conducted. Subgroup analysis based on predicted prognosis at randomisation showed that IPCD appeared to reduce the risk of DVT and probably improve survival in all immobile

Treatment effect duration:[(a)] 6 months **Discounting:** Costs: n/a ; Outcomes: n/a	**Intervention 2: (n=1438)** Thigh length IPC in addition to usual care. IPC the IPC system used as the Kendall SCD™ express sequential compression (Covedien Ltd, Mansfield, MA, USA) with thigh length sleeves worn continuously on both legs for 30 days or next CDU (if >30 days) or untill the patient was independently mobile, discharged from randomising hospital or refused to wear the sleeves or the staff became concerned about his/her skin condition.			stroke patients except those in the fifth quintile (those with best prognosis). The authors concluded that IPC is likely to be most effective in the subgroups of immobile stroke patients In the three intermediate quintiles.
Data sources				
Health outcomes: 6 month quality of life data gathered during associated trial. Base-line utility modelled using a Bayesian Network incorporating data from the other CLOTS studies because of the questionable validity of asking patients or carers to rate their quality of life shortly after admission to hospital with a severe stroke. **Quality-of-life weights:** EQ-5D-3L UK tariff. **Cost sources:** NHS reference costs for English centres, Scottish Health Service Costs for Scottish centres.				
Comments				
Source of funding: University of Edinburgh, NHS Lothian and NIHR HTA Program. Covidien LtD provided IPCs **Limitations:**Most of the cost difference was derived from a per diem amount applied to a non- significant difference in length of stay rather than the actual cost of the hospital stay. Important costs were excluded from the analysis such as readmissions, post-hospital care, deep vein thrombosis, and pulmonary embolism. The timeframe was only 6 months which is unlikely to be sufficient to capture important cost and health consequences. The statistical methods used to estimate quality of life at baseline was experimental and had not been independently verified. The EQ-5D-3L generic quality of life measurement tool was known to have limitations in detecting small functional improvements in severely disabled people. There is a high degree of uncertainty around the estimates provided.				
Overall applicability:[(b)] Directly applicable **Overall quality**[(c)] Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D-3L: Euroqol 5 dimensions 3 levels (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; IPC: intermittent pneumatic compression; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

J.13 Acutely ill medical patients

Study	[National Clinical Guideline Centre 2010[666]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design**: Decision analytic model **Approach to analysis:** A decision tree model was developed based on the results of a systematic literature review and a network meta-analysis. **Perspective:** UK NHS and PSS **Time horizon:** VTEs and major bleeding events modelled for the acute period 10 days). QALYs and health service costs arising from these events are modelled over the patient's lifetime **Treatment effect**	**Population:** Adult (18 years or older) admitted as general medical admissions to hospitals in England. **Cohort settings:** Start age: 74 years Male: 47% **Intervention 1:** No prophylaxis **Intervention 2:** LMWH (average of dalteparin 5000 units sc daily) and enoxaparin (4000 units subcutaneously daily) **Intervention 3:** UFH (5000 units three times daily) **Intervention 4:**	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR) **Currency & cost year:** 2009 UK pounds **Cost components incorporated:** Pharmacological prophylaxis costs, prophylaxis testing, nurse time, VTE diagnosis and treatment costs, other events treatment costs (i.e. stroke, PTS, CTEPH, major bleeding, reoperation)	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR)	**Incremental net monetary benefit (INMB)** (pa) **Intervention 1:** £0 (comparator) **Intervention 2:** £328 **Intervention 3:** £118 **Intervention 4:** -£61 Probability cost-effective (£20K threshold): **Intervention 1:** 1.7% **Intervention 2:** 72.3% **Intervention 3:** 17.7% **Intervention 4:** 8.3% **Analysis of uncertainty:** Deterministic and probabilistic sensitivity analyses were performed. The deterministic SAs explored the impact of changing the incidence of CTEPH and PTS and their costs, including HIT, changing its incidence, lower costs for LMWH, changing fatality rate after PE and MB and change the cost effectiveness threshold.

duration:[(a)] 10 days **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	Fondaparinux sodium (2.5 mg subcutaneously)			A two-way threshold analysis exploring the impact of baseline risk for both major bleeding and PE was also undertaken. In all SAs, the most cost effective strategy remained the same (LMWH), except where high bleeding baseline risk and low PE baseline risk were used, where no prophylaxis was the most cost effective strategy.
Data sources				
Health outcomes: baseline events were obtained from the no prophylaxis arm of the RCTs included in the systematic review and NMA that informed the model. Relative treatment effects for DVT (symptomatic and asymptomatic), PE (symptomatic) and major bleeding. **Quality-of-life weights:** utilities based on the EQ-5D UK tariff were sourced from the published literature and previous guidelines. **Cost sources:** standard sources on unit costs in the UK were used including the drug tariff, the NHS reference costs and the BNF.				
Comments				
Source of funding: National Institute for Health and Care Excellence (NICE). **Limitations:** Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context. The relative treatment effect applied to all VTE events in the model is the relative treatment effect obtained from the DVT NMA.				
Overall applicability:[(b)] Directly applicable **Overall quality**[(c)] Potentially serious limitations				

Abbreviations: BNF: British National Formulary; 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; da: deterministic analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HIT: Heparin induced thromboembolism; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; NR: not reported; NMA: network meta-analysis; pa: probabilistic analysis; PE: pulmonary embolism; QALYs: quality-adjusted life years; SA: sensitivity analysis; UFH: unfractionated heparin.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**[Millar 2016[640]]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CCA (health outcomes: years of	**Population:** Adult patients admitted to	**Total cost[(b)] (mean per patient):**	**Deaths[(b)] (mean per patient):**	**ICER:** DVTs

life lost, non-fatal VTE events avoided) **Study design:** decision tree model **Approach to analysis:** a decision tree model was designed based on the results of the PREVENT trial. **Perspective:** Australian public health care system **Follow-up:** inpatient admission period **Treatment effect duration:**[a] same as follow-up **Discounting:** Costs: n/a ; Outcomes: 3%	Australian hospital as medical inpatients. **Cohort settings:** Start age: 74 years Male: NR **Intervention 1:** No VTE prophylaxis. **Intervention 2:** VTE prophylaxis using LMWH (Enoxaparin 40 mg/day). Three levels of eligibility for prophylaxis were examined: 2.a. 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) 2.b. Intermediate: where patients with strong and moderate risk factors,	Intervention 1: £29 Intervention 2-Restricted : £26 Intervention 2-Intermediate : £30 Intervention 2-Broad : £39 **Currency & cost year:** Australian dollars presented here as 2014 UK pounds[c] **Cost components incorporated** LMWH prophylaxis Treatment costs for DVT, PE, PTS and major bleeds Nursing time Hospital costs GP visits Monitoring	Intervention 1: 0.0004 Intervention 2: Restricted: 0.0005 Intermediate: 0.0006 Broad: 0.0009 **Total DVTs[b] (mean per patient):** Intervention 1: 0.0043 Intervention 2: Restricted: 0.0025 Intermediate: 0.0024 Broad: 0.0021 **Total PEs[b] (mean per patient):** Intervention 1: 0.0023 Intervention 2: Restricted: 0.0020 Intermediate: 0.0020 Broad: 0.0019	1. No VTE Prophylaxis: dominated 2.a (Restricted eligibility): baseline 2.b. (Intermediate eligibility): extendedly dominated (da) 2.c. (Broad eligibility) vs 2.a. (restricted eligibility): £29,861 per DVT averted (da) **PEs** 1. No VTE Prophylaxis: dominated 2.a (Restricted eligibility): baseline 2.b. (Intermediate eligibility): extendedly dominated (da) 2.c. (Broad eligibility) vs 2.a. (restricted eligibility): £170,827 per DVT averted (da) **Death** 1. No VTE Prophylaxis: £30,000 per death averted 2.a (Restricted eligibility): baseline 2.b. (Intermediate eligibility): dominated (da) 2.c. (Broad eligibility) vs 2.a. (restricted eligibility): dominated (da) **Analysis of uncertainty:** 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.

	such as cardiac or respiratory failure, sepsis or inflammation, are given prophylaxis (~ 40% of all inpatient admissions) 2.c. 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)			

Data sources
Health outcomes: Data on symptomatic DVTs, PEs and major bleeding were based on the results of the PREVENT trial. **Quality-of-life weights:** n/a. **Cost sources:** national unit costs were used and these were obtained from the Medicare Benefits Schedule, Australia and the Department of Health and Ageing, Canberra.
Comments
Source of funding: NR. **Limitations:** 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. 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.
Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] Potentially serious limitations

Abbreviations: CCA: cost-consequency analysis; 95% CI: 95% confidence interval; da: deterministic analysis; DVT: Deep vein thrombosis; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; n/a: not applicable; NR: not reported; pa: probabilistic analysis; PE: pulmonary embolism; QALYs: quality-adjusted life years; VTE: venous thromboembolism.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Calculated by NGC based on 1,458,600 inpatient admissions.

(c) Converted using 2014 purchasing power parity[715]

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**[Wilbur 2011[1007]]**

Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: CCA (health outcome: DVT [distal or proximal, not progressing to PE], combined toward events (PE, major bleed and death)) **Study design:** probabilistic decision analytic model **Approach to analysis:** Decision tree model to simulate the hospital stay of medical patients with results for cancer patients reported as subgroup analysis. **Perspective:** Canadian institutional (i.e. hospital perspective) **Time horizon:** 7 days **Treatment effect duration:**[(a)] 7 days **Discounting:** Costs: NA ; Outcomes: NA	**Population:** Hospital adult internal medicine patients. **Cohort settings:** Start age: NR Male: NR **Intervention 1:** UFH (5000 U, twice daily [bid], SC]) initiated on day 1 of hospital stay and continued for 7 days. **Intervention 2:** LMWH (enoxaparin 40 mg, once daily [od], administered subcutaneously [SC]) initiated on day 1 of hospital stay and continued for 7 days (mean LOS for internal medicine patient in the institution).	**Total costs (mean per patient):** Intervention 1: £2,892 Intervention 2: £2,896 Incremental (2−1): £4 (95% CI: NR; p=NR) **Cancer subgroup:** **Total costs (mean per patient):** Intervention 1: £2,908 Intervention 2: £2,910 Incremental (2−1): £2 (95% CI: NR; p=NR) **Currency & cost year:** 2009 Canadian dollars (presented here as 2009 UK pounds[(b)]) **Cost components incorporated:** Only direct medical costs included: -Thromboprophylaxis drug costs -VTE diagnosis - VTE treatment	**True DVT events (mean per patient):** Intervention 1: 0.024 events Intervention 2: 0.021 events Incremental (2−1): - 0.003 events (95% CI: NR; p=NR) **Untoward events (mean per patient):** Intervention 1: 0.0115 events Intervention 2: 0.0102 events Incremental (2−1): - 0.0013 events (95% CI: NR; p=NR) **PE events (mean per patient):** Intervention 1: 0.005 events Intervention 2: 0.004 events Incremental (2−1): - 0.001 events (95% CI: NR; p=NR) **Major bleeding events (mean per patient):**	**ICER (Intervention 2 versus Intervention 1):** £1,116 **per DVT averted** (da) 95% CI: NR £3,726 **per untoward event averted** (da) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NA **Cancer subgroup:** **ICER (Intervention 2 versus Intervention 1):** £287 **per DVT averted** (da) 95% CI: NR £1,037 **per untoward event averted** (da) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NA **Analysis of uncertainty:** One way sensitivity analyses were conducted to examine the robustness of the model results to changes in the following parameters' values:

		-pharmacy and nursing time For administering and preparing the medications -hospitalisation costs -costs of treating major bleeding (extended length of stay, treatments and other management costs)	Intervention 1: 0.0005 events Intervention 2: 0.0002 events Incremental (2−1): - 0.0003 events (95% CI: NR; p=NR) **Death (mean per patient):** Intervention 1: 0.006 events Intervention 2: 0.006 events Incremental (2−1): 0.000 events (95% CI: NR; p=NR) **Cancer subgroup:** **True DVT events (mean per patient):** Intervention 1: 0.037 events Intervention 2: 0.031 events Incremental (2−1): - 0.006 events (95% CI: NR; p=NR) **Untoward events (mean per patient):** Intervention 1: 0.044	-acquisition cost of LMWH (using the cost of other LMWHs included in the systematic review: dalteparin and nadroparin) -costs of managing PE and major bleeding -baseline rate of DVT -probability of progression to PE in absence of treatment -assuming alternative LOS PSA was also conducted, assigning distributions for each model parameter . It was conducted using "untoward events averted as the effectiveness outcome). The SAs were consistent across the different scenarios considered. None of the SAs were conducted for the cancer subgroup.

events Intervention 2: 0.037 events Incremental (2–1): - 0.007 events (95% CI: NR; p=NR) **PE events (mean per patient):** Intervention 1: 0.007 events Intervention 2: 0.006 events Incremental (2–1): - 0.001 events (95% CI: NR; p=NR) **Major bleeding events (mean per patient):** Intervention 1: 0.0006 events Intervention 2: 0.0003 events Incremental (2–1): - 0.0003 events (95% CI: NR; p=NR) **Death (mean per patient):** Intervention 1: 0.006 events Intervention 2: 0.006				

			events Incremental (2−1): 0.000 events (95% CI: NR; p=NR)	

Data sources

Health outcomes: Baseline risk for the UFH group and relative treatment effect of LMWH vs UFH for DVT and major bleeding were based on a published review of the literature (Mismetti 2000 [644]) while probabilities of PE and death were sourced from other published papers . Heparin induced thrombocytopenia (HIT), PTS, minor bleeding were not modelled. **Quality-of-life weights:** NA. **Cost sources:** Costs of prophylaxis were obtained from the Vancouver general Hospital Pharmacy. Costs of investigations and tests were obtained from the British Columbia Medical Association Guide to Fees. Nursing and Pharmacy labour costs were based on estimate of time spent in preparation and administration of prophylaxis. The pharmacist wage rate was obtained from the Health Sciences Association of British Columbia while the nurse wage rate was obtained from the British Columbia Nurses' Union. Hospitalisation costs were calculated by multiplying length of stay by the per-diem cost. Costs of treating major bleeding were based on published studies.

Comments

Source of funding: no funding received. **Limitations:** 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. 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. **Other:** Investigations to confirm DVT were Doppler ultrasound, examination of the legs, D-Dimer testing and Chest X-ray. Investigations to confirm symptomatic PE are electrocardiogram (ECG) and chest compound tomography (CT) scan with contrast. Treatment strategy for detected VTE would be LMWH and oral anticoagulation with warfarin (initiated at 5 mg orally daily and titrated to international normalised ration (INR) 2-3.

Overall applicability:(c) partially applicable **Overall quality**(d) potentially serious limitations

Abbreviations: bid: twice daily; CCA: cost-consequences analysis; 95% CI: 95% confidence interval; da: deterministic analysis; DVT: Deep vein thrombosis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HIT: heparin induced thrombocytopenia; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; LOS: length of stay; NA: not applicable; NR: not reported; od: once daily; pa: probabilistic analysis; PE: pulmonary embolism; PTS: post-thrombotic syndrome; QALYs: quality-adjusted life years; SC: subcutaneous; UFH: un-fractionated heparin; VTE: venous thromboembolism.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2009 purchasing power parities[715]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

J.14 Cancer

Study	[Chalayer 2016[165]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision analytic model **Approach to analysis:** A decision tree based on results of Palumbo 2011 clinical trial[724]. **Perspective:** France National Health Insurance System **Time horizon:** 6 months **Treatment effect duration:**[(a)] 6 months **Discounting:** Costs: n/a ; Outcomes: n/a	**Population:** Patients newly diagnosed with multiple myeloma treated with protocols including thalidomide **Cohort settings:** Start age: NR Male: NR **Intervention 1:** Aspirin (100mg/day) for 3 months. **Intervention 2:** LMWH standard dose, standard duration) (Enoxaparin 40mg/day) for 6 months.	**Total costs (mean per patient):** Intervention 1: £230 Intervention 2: £1,283 Incremental (2−1): £1,053 (95% CI: NR; p=NR) **Currency & cost year:** 2013 Euros (presented here as 2013 UK pounds[(b)]) **Cost components incorporated:** Hospitalisation GP visits Home nursing Laboratory investigation Radiologic procedures Drugs	**QALYs (mean per patient):** Intervention 1: 0.300 Intervention 2: 0.299 Incremental (2−1): -0.001 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 1 dominant (less costly and more effective)(pa) 95% CI: n/a Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** None of the sensitivity analyses undertaken changed the conclusion.
Data sources				
Health outcomes: data on baseline risks and relative treatment effects are based on a single RCT (Palumbo 2011[724]). These outcomes included DVT, PE, stroke, acute MI, major bleeding and sudden death. **Quality-of-life weights:** EQ-5D index values were used. **Cost sources:** National unit cost sources were used including National reimbursement database and Vidal drug compendium.				
Comments				
Source of funding: None. **Limitations:** Some uncertainty regarding the applicability of unit costs from France in 2013 to current NHS context. The model does not incorporate any long-term consequences such as CTEPH or PTS. Baseline risk and relative treatment effects are based on a single open-label trial, so by definition, does not reflect all available evidence. Costs of LMWH administration might be underestimated.				

Overall applicability:[c] Partially applicable **Overall quality**[d] potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis; PTS: post-thrombotic syndrome; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2013 purchasing power parities[715]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

J15 Patients with central venous catheters

No relevant economic evaluations were identified.

J16 Palliative care

No relevant economic evaluations were identified.

J17 Critical care

No relevant economic evaluations were identified.

J18 Pregnant women and women up to 6 weeks postpartum

No relevant economic evaluations were identified.

J19 People with psychiatric illness

No relevant economic evaluations were identified.

J120 Anaesthesia

114 No relevant economic evaluations were identified.

J121 Lower limb immobilisation

116 No relevant economic evaluations were identified.

J122 Fragility fractures of the pelvis, hip and proximal femur

Study	[National Clinical Guideline Centre 2010[666]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design**: Decision analytic model **Approach to analysis:** A decision tree model was developed based on the results of a systematic literature review and a network meta-analysis. **Perspective:** UK NHS and PSS **Time horizon:** VTEs and major bleeding events modelled for the acute period (10 days). QALYs and health service costs arising from these events are modelled over	**Population:** Adults admitted for hip fracture surgery in England. **Cohort settings: (HES data)** Start age: 82 years Male: 23% **Interventions:** 1. Fondaparinux sodium (2.5 mg subcutaneously) 2.Warfarin variable dose (adjusted to INR range 2 to 3, average dose 4mg/day) 3. LMWH (average of dalteparin 5000 units subcutaneous daily) and enoxaparin (4000 units subcutaneous daily) 4. UFH (5000 units three times daily)	**Total costs (mean per patient):** NR Incremental (2−1): NR (95% CI: NR; p=NR) **Currency & cost year:** 2009 UK pounds **Cost components incorporated:** Pharmacological prophylaxis costs, prophylaxis testing, nurse time, VTE diagnosis and treatment costs, other events treatment costs (i.e. stroke, PTS, CTEPH, major bleeding, reoperation)	**QALYs (mean per patient):** NR Incremental (2−1): NR (95% CI: NR; p=NR)	**Incremental net monetary benefit (INMB)** (pa) Intervention 1: £2148 (rank 1) Intervention 2: £1830 (rank 2) Intervention 3: £1711 (rank 3) Intervention 4: £1465 (rank 4) Intervention 5: £999 (rank 5) Intervention 6: £558 (rank 6) Intervention 7: £0 (rank 7) Probability cost-effective (£20K threshold): Intervention 1: 85% Intervention 2: 4.2% Intervention 3: 4.5% Intervention 4: 0.6% Intervention 5: 5.7% Intervention 6: 0.0% Intervention 7: 0.0%

Study	[National Clinical Guideline Centre 2010[666]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
the patient's lifetime **Treatment effect duration:**[(a)] 10 days **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	5. IPCD-FID 6.Aspirin (High dose) 7. No prophylaxis			**Analysis of uncertainty:** Deterministic and probabilistic sensitivity analyses were performed. The deterministic SAs explored the impact of changing the incidence of CTEPH and PTS and their costs, including HIT, changing its incidence, lower costs for LMWH, changing fatality rate after PE and MB and change the cost effectiveness threshold. In all analyses, fondaparinux remained as the most cost-effective strategy. A two-way threshold analysis exploring the impact of baseline risk for both major bleeding and PE was also undertaken. It showed that as the risk of bleeding increases and the risk of PE decreases, LMWH becomes the most cost-effective option.
Data sources				
Health outcomes: baseline events were obtained from the no prophylaxis arm of the RCTs included in the systematic review and NMA that informed the model. Relative treatment effects for DVT (symptomatic and asymptomatic), PE (symptomatic) and major bleeding. **Quality-of-life weights:** utilities based on the EQ-5D UK tariff were sourced from the published literature and previous guidelines. **Cost sources:** standard sources on unit costs in the UK were used including the drug tariff, the NHS reference costs and the BNF.				
Comments				
Source of funding: National Institute for Health and Care Excellence (NICE). **Limitations:** Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context. Some of the interventions are not included in the current clinical review, for example aspirin (high dose), warfarin (variable dose) and UFH. The relative treatment effect applied to all VTE events in the model is the relative treatment effect obtained from the DVT NMA.				
Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] Minor limitations				

Abbreviations: BNF: British National Formulary; 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; da: deterministic analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); FID: foot impulse devices; HES: Hospital Episode statistics; HIT: Heparin induced thromboembolism; ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; IPCD: intermittent pneumatic compression

devices; LMWH: low molecular weight heparin; NR: not reported; NMA: network meta-analysis; pa: probabilistic analysis; PE: pulmonary embolism; QALYs: quality-adjusted life years; SA: sensitivity analysis; UFH: unfractionated heparin.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**[National Clinical Guideline Centre 2010[666]]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design**: Decision analytic model **Approach to analysis:** A decision tree model was developed based on the results of a systematic literature review and a direct meta-analysis of the trials that randomised patients at the point of discharge. **Perspective:** UK NHS and PSS **Time horizon:** VTEs and major bleeding events modelled for the acute period 28 days). QALYs and health service costs arising from these events are modelled over the patient's lifetime **Treatment effect**	**Population:** Adults admitted for hip fracture surgery in England. **Cohort settings: (HES data)** Start age: 82 years Male: 23% **Interventions 1:** No post discharge prophylaxis (it is not clear whether prophylaxis was given during the initial hospital stay) **Intervention 2:** Post-discharge prophylaxis with fondaparinux 2.5 mg given subcutaneously once daily.	**Total costs (mean per patient):** NR Incremental (2−1): NR (95% CI: NR; p=NR) **Currency & cost year:** 2009 UK pounds **Cost components incorporated:** Pharmacological prophylaxis costs, prophylaxis testing, nurse time, VTE diagnosis and treatment costs, other events treatment costs (i.e. stroke, PTS, CTEPH, major bleeding, reoperation)	**QALYs (mean per patient):** NR Incremental (2−1): NR (95% CI: NR; p=NR)	**Incremental net benefit (INB)** (pa) Intervention 1: £0 Intervention 2: £239 Probability cost-effective (£20K threshold): Intervention 1: 8.0% Intervention 2: 92.0% **Analysis of uncertainty:** Deterministic and probabilistic sensitivity analyses were performed. The deterministic SAs explored the impact of changing the incidence of CTEPH and PTS and their costs, including HIT, changing its incidence, lower costs for LMWH, changing fatality rate after PE and MB and change the cost effectiveness threshold. In all SAs, the most cost effective strategy remained the same (fondaparinux). A two-way threshold analysis exploring the impact of baseline risk for both major bleeding and PE was also

Study	[National Clinical Guideline Centre 2010[666]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
duration:[(a)] 28 days **Discounting:** Costs: 3.5% ; Outcomes: 3.5%				undertaken. It showed that as the risk of bleeding increases and the risk of PE decreases, no prophylaxis becomes the most cost-effective option.
Data sources				
Health outcomes: baseline events were obtained from the no prophylaxis arm of the RCTs included in the systematic review and direct meta-analysis that informed the model. Relative treatment effects for DVT (symptomatic and asymptomatic), PE (symptomatic) and major bleeding. **Quality-of-life weights:** utilities based on the EQ-5D UK tariff were sourced from the published literature and previous guidelines. **Cost sources:** standard sources on unit costs in the UK were used including the drug tariff, the NHS reference costs and the BNF.				
Comments				
Source of funding: National Institute for Health and Care Excellence (NICE). **Limitations:** Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context. The relative treatment effect applied to all VTE events in the model is the relative treatment effect obtained from the DVT MA.				
Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] potentially serious limitations				

Abbreviations: BNF: British National Formulary; 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; da: deterministic analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HES: Hospital Episode statistics; HIT: Heparin induced thromboembolism; ICER: incremental cost-effectiveness ratio; NR: not reported; NMA: network meta-analysis; pa: probabilistic analysis; PE: pulmonary embolism; QALYs: quality-adjusted life years; SA: sensitivity analysis.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

J.23 Elective hip replacement

No relevant economic evaluations were identified.

J.24 Elective knee replacement

No relevant economic evaluations were identified.

J25 Non-arthroplasty orthopaedic knee surgery

No relevant economic evaluations were identified.

J26 Foot and ankle orthopaedic surgery

No relevant economic studies were identified.

J27 Upper limb orthopaedic surgery

No relevant health economic studies were identified.

J28 Spinal surgery

No relevant health economic studies were identified.

J29 Cranial surgery

No relevant health economic studies were identified.

J30 Spinal injury

No relevant health economic studies were identified.

J.31 Major trauma

Study	[Carter Chiasson 2009[175]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision analytic model **Approach to analysis:** A Markov analysis using weekly cycles over lifetime (30 years) time horizon. **Perspective:** Canadian health care purchaser. **Time horizon:** lifetime **Treatment effect duration:**[(a)] 2 weeks **Discounting:** Costs: 5% ; Outcomes: 5%	**Population:** Adult (>/= 15 years)Trauma patients with severe injuries admitted to the ICU who were believed to have a contraindication to pharmacological VTE prophylaxis for up to 2 weeks because of a risk of major bleeding. **Cohort settings:** Start age: 39.3 years Male: 76% **Intervention 1:** Pneumatic compression devices (IPCD) and expectant management alone during the first 2 weeks. **Intervention 2: (results not reported here)**	**Total costs (mean per patient):** Intervention 1: £35,571 Intervention 3: £36,529 Incremental (3−1): £975 (95% CI: NR; p=NR) **Currency & cost year:** 2007 Canadian dollars (presented here as 2007 UK pounds[(b)]) **Cost components incorporated:** Intervention costs (including VCF insertion) Hospital stay Readmissions Management of adverse events (mainly major bleeding) DVT and VTE diagnosis and treatment	**QALYs (mean per patient):** Intervention 1: 6.9 Intervention 3: 6.9 Incremental (3−1): 0.0 (95% CI: NR; p=NR)	**ICER (Intervention 3 versus Intervention 1):** N/A [VCF more costly and equally effective] 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** A wide range of one-way sensitivity analyses was undertaken including changing the following parameters: -risk of DVT -risk of PE for patient with DVT -risk of mortality associated with PE -risk of proximal DVT after insertion of VCF -inclusion of the cost of VCF removal for all patients who had no VTE at discharge. None of the SAs changed the conclusion from the base case analysis.

	IPCD as well as weekly Serial Doppler ultrasound (SDU) screening for the duration of hospitalisation beginning in the first week of ICU admission. **Intervention 3:** Prophylactic insertion of vena-cava filter (VCF).			
Data sources				
Health outcomes: Baseline risks of proximal DVT and PE were based on published data from observational cohort study and a randomised trial. Relative efficacy of VCF was based on data from single RCT identified through a systematic review of the literature. **Quality-of-life weights:** Not reported. **Cost sources:** Both local and National sources of unit costs were used, including the Alberta Drug Benefit List, as well as published studies.				
Comments				
Source of funding: None. **Limitations:** Uncertainty regarding the applicability of unit costs from Canada, in 2007 to current NHS context. The discount used is 5% for both costs and outcomes; however, this was tested in a sensitivity analysis with a range of 0-6%. It is not clear which utility measure was used to derive the utility values used in the model. The health states included in the long term of the model does not seem to include CTEPH as a complication of PE. Baseline risks as well as relative effectiveness are based on the results of an observational cohort and single RCT so by definition, not reflective of all the evidence in this area. Both local and national unit costs were used in the analysis, so may not be generalisable. Utility values were not tested in sensitivity analysis.				
Overall applicability:[(c)] Partially applicable **Overall quality**[(d)] Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; N/a: not applicable; NR: not reported; PCD: pneumatic compression device; QALYs: quality-adjusted life years, RCT: Randomised controlled trial; SAs: sensitivity analyses; SDU: serial Doppler Ultrasound; VCF: vena-cava filter.

(d) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(e) Converted using 2007 purchasing power parities[715]

(f) Directly applicable / Partially applicable / Not applicable

(g) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**[Lynd 2007[590]]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**

Economic analysis: CCA (health outcomes: life-years gained (LYG), DVT averted, PE averted, MB, mortality) **Study design:** Decision analytic model **Approach to analysis:** Decision tree model run probabilistically. **Perspective:** Canadian Heath care payer **Time horizon:** lifetime **Treatment effect duration:**[(a)] NR **Discounting:** Costs: 0% ; Outcomes: 5%	**Population:** Patients with major trauma (trauma score of =>9) **Cohort settings:** Start age: 39 years Male: 72% **Intervention 1:** UFH 5000 units once daily. **Intervention 2:** LMWH (enoxaparin 30 mg once daily).	**Total costs (mean per patient):** Intervention 1: £6,572 Intervention 2: £6,619 Incremental (2−1): £47 (95% CI: NR; p=NR) **Currency & cost year:** 2003 Canadian dollars (presented here as 2003 UK pounds(b)) **Cost components incorporated:** Direct costs incurred during the hospital stay including: a) Mean total cost of hospital stay for treated patients b) Mean cost of diagnosis and treatment of DVT and PE c) Additional cost of prophylaxis due to major bleeds	**LYG (mean per patient):** Intervention 1: 17.05 Intervention 2: 16.92 Incremental (2−1): - 0.13 (95% CI: NR; p=NR) **DVT (mean per patient):** Intervention 1: 0.147 Intervention 2: 0.061 Incremental (2−1): - 0.086 (95% CI: NR; p=NR) **PE (mean per patient):** Intervention 1: 0.003 Intervention 2: 0.0012 Incremental (2−1): -0.0018 (95% CI: NR; p=NR) **MB (mean per patient):** Intervention 1: 0.0084 Intervention 2: 0.0388 Incremental (2−1): 0.0018 (95% CI: NR; p=NR) **Mortality (mean per patient):** Intervention 1:0.01 Intervention 2: 0.003 Incremental (2−1): - 0.007 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1)-DVT primary outcome:** £553 per DVT averted (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR Probability Intervention 2 cost-effective (£10,435 ($20,000 Canadian dollars (2003) threshold): 93% **ICER (Intervention 2 versus Intervention 1)-LYG primary outcome:** Intervention 2 dominated (less effective and more costly) (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR Probability Intervention 2 cost-effective (£10,435 ($20,000 Canadian dollars (2003) threshold): 9% **Analysis of uncertainty:** PSA as well as 1-way, 2-way DSA. All analyses had minor effects on the ICERs with UFH remaining dominant when LYG was used as the primary outcome.
Data sources				

Health outcomes: A systematic review of the literature was undertaken but only a single RCT (Geerts 1996[340]) was retrieved and used as the source of data on baseline risk and relative efficacy. **Quality-of-life weight:** N/A. **Cost sources:** local unit costs were used for pharmacological prophylaxis. Ontario Nurses Union collective bargaining agreement and London Health Sciences Centre, London, Ontario were the reported unit cost sources.	
Comments	
Source of funding: Canadian Institutes for Health Research post-doctoral fellowship; Michael Smith Foundation for Health Research; Heart and Stroke Foundation of Ontario. **Limitations:** Uncertainty regarding the applicability of unit costs from Canada, in 2003 to current NHS context. The discount used is 5% for outcomes; however, this was tested in a sensitivity analysis with a range of 3-7%. QALYs were not used as outcome. The health states included in the long term of the model do not include distal DVT, CTEPH and PTS. Baseline risks as well as relative effectiveness are based on the results of a single RCT (Geerts 1996[340]) so by definition, not reflective of all the evidence in this area. Both local and national unit costs were used in the analysis, so may not be generalisable.	
Overall applicability:[(c)] partially applicable **Overall quality**[(d)] potentially serious limitations	

Abbreviations: CCA: cost-consequences analysis; 95% CI: 95% confidence interval; CTEPH: Chronic thromboembolic hypertension; da: deterministic analysis; DSA: deterministic sensitivity analysis; DVT: deep vein thrombosis; LYG: life-years gained; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; PE: pulmonary embolism; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life year; PTS: post-thrombotic syndrome; RCT: randomised controlled trial.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2003 purchasing power parities[715]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

J.32 Abdominal surgery (excluding bariatric surgery)

Study	[National Clinical Guideline Centre 2010[666]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design**: Decision analytic model **Approach to analysis:** A decision tree model was developed based on the	**Population:** Adult (18 years or older) admitted for elective abdominal surgery to hospitals in England. **Cohort settings:** Start age: 60 years Male: 50%	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR)	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR)	**Incremental net benefit (INB)** (pa) **Intervention 1:** £488 **Intervention 2:** £464 **Intervention 3:** £408 **Intervention 4:** £348 **Intervention 5:** £347 **Intervention 6:** £314

results of a systematic literature review and a network meta-analysis. **Perspective:** UK NHS and PSS **Time horizon:** VTEs and major bleeding events modelled for the acute period 10 days). QALYs and health service costs arising from these events are modelled over the patient's lifetime **Treatment effect duration:**[(a)] 10 days **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	**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	**Currency & cost year:** 2009 UK pounds **Cost components incorporated:** Pharmacological prophylaxis costs, prophylaxis testing, nurse time, VTE diagnosis and treatment costs, other events treatment costs (i.e. stroke, PTS, CTEPH, major bleeding, reoperation)		**Intervention 7:** £241 **Intervention 8:** £127 **Intervention 9:** £104 **Intervention 10:** £75 **Intervention 11:** £0 **Intervention 12:** -£694 Probability cost-effective (£20K threshold): **Intervention 1:** 38.3% **Intervention 2:** 24.5% **Intervention 3:** 4.1% **Intervention 4:** 10.1% **Intervention 5:** 0.3% **Intervention 6:** 0.7% **Intervention 7:** 0.0% **Intervention 8:** 0.2% **Intervention 9:** 0.5% **Intervention 10:** 0.0% **Intervention 11:** 0.0% **Intervention 12:** 21.3% **Analysis of uncertainty:** Deterministic and probabilistic sensitivity analyses were performed. The deterministic SAs explored the impact of changing the incidence of CTEPH and PTS and their costs, including HIT, changing its incidence, lower costs for LMWH, changing fatality rate after PE and MB and change the cost effectiveness threshold. A two-way threshold analysis exploring the impact of baseline risk for both major

				bleeding and PE was also undertaken. There was only one situation in the deterministic sensitivity analysis in which the most cost effective strategy changed: 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.
Data sources				
Health outcomes: baseline events were obtained from the no prophylaxis arm of the RCTs included in the systematic review and NMA that informed the model. Relative treatment effects for DVT (symptomatic and asymptomatic), PE (symptomatic) and major bleeding. **Quality-of-life weights:** utilities based on the EQ-5D UK tariff were sourced from the published literature and previous guidelines. **Cost sources:** standard sources on unit costs in the UK were used including the drug tariff, the NHS reference costs and the BNF.				
Comments				
Source of funding: National Institute for Health and Care Excellence (NICE). **Limitations:** Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context. The relative treatment effect applied to all VTE events in the model is the relative treatment effect obtained from the DVT NMA.				
Overall applicability:(b) Partially applicable **Overall quality**(c) Potentially serious limitations				

Abbreviations: AES: Anti-embolism stockings; BNF: British National Formulary; 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; da: deterministic analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); 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; NR: not reported; NMA: network meta-analysis; pa: probabilistic analysis; PE: pulmonary embolism; QALYs: quality-adjusted life years; SA: sensitivity analysis; UFH: unfractionated heparin; VKA: Vitamin K antagonists.

(d) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(e) Directly applicable / Partially applicable / Not applicable

(f) Minor limitations / Potentially serious limitations / Very serious limitations

Study	[National Clinical Guideline Centre 2010[666]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design**: Decision analytic model **Approach to analysis:** A decision tree model was developed based on the results of a systematic literature review and a network meta-analysis. **Perspective:** UK NHS and PSS **Time horizon:** VTEs and major bleeding events modelled for the acute and post discharge period. QALYs and health service costs arising from these events are modelled over the patient's lifetime **Treatment effect duration:**[(a)] 21 days **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	**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) **Cohort settings:** Start age: 60 years Male: 50% **Intervention 1:** No post discharge prophylaxis **Intervention 2:** LMWH initiated post discharge and continued for 21 days.	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR) **Currency & cost year:** 2009 UK pounds **Cost components incorporated:** Pharmacological prophylaxis costs, prophylaxis testing, nurse time, VTE diagnosis and treatment costs, other events treatment costs (i.e. stroke, PTS, CTEPH, major bleeding, reoperation)	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR)	**Incremental net benefit (INB)** (pa) **Intervention 1:** £0 (comparator) **Intervention 2:** £49 Probability cost-effective (£20K threshold): **Intervention 1:** 22.5% **Intervention 2:** 77.5% **Analysis of uncertainty:** Deterministic and probabilistic sensitivity analyses were performed. The deterministic SAs explored the impact of changing the incidence of CTEPH and PTS and their costs, including HIT, changing its incidence, lower costs for LMWH, changing fatality rate after PE and MB and change the cost effectiveness threshold. A two-way threshold analysis exploring the impact of baseline risk for both major bleeding and PE was also undertaken. 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.
Data sources				
Health outcomes: baseline events were obtained from the no prophylaxis arm of the RCTs included in the systematic review and MA that informed the model. Relative treatment effects for DVT (symptomatic and asymptomatic), PE (symptomatic) and major bleeding. **Quality-of-life weights:** utilities based on the EQ-5D UK tariff were				

sourced from the published literature and previous guidelines. **Cost sources:** standard sources on unit costs in the UK were used including the drug tariff, the NHS reference costs and the BNF.	
Comments	
Source of funding: National Institute for Health and Care Excellence (NICE). **Limitations:** Some uncertainty regarding the applicability of unit costs from 2009 to current NHS context. The relative treatment effect applied to all VTE events in the model is the relative treatment effect obtained from the DVT MA.	
Overall applicability:[(b)] Directly applicable	**Overall quality**[(c)] Potentially serious limitations

Abbreviations: AES: Anti-embolism stockings ;BNF: British National Formulary; 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; da: deterministic analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); FID: foot impulse devices; HIT: Heparin induced thromboembolism; ICER: incremental cost-effectiveness ratio; LMWH: low molecular weight heparin; NR: not reported; NMA: network meta-analysis; pa: probabilistic analysis; PE: pulmonary embolism; QALYs: quality-adjusted life years; SA: sensitivity analysis;

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**[Wade 2015[985]]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Systematic review and economic model, including value of information analysis. **Approach to analysis:** a two stage modelling approach, a decision tree for the acute phase (up to 14 days post-surgery) followed by Markov models for the long term phase with annual cycles.	**Population:** Patients undergoing any general surgery (subgroups considered were THR, TKR, general surgery for high risk patients, general surgery for medium risk patients and general surgery for low risk patients. The results presented here are for the general surgery subgroups [high, medium and low risk patients]) **Cohort settings:** Start age: 60 years	**Total costs (mean per patient):** **High risk patients:** Intervention 1: £521 Intervention 2: £522 Intervention 3 : £345 **Intermediate risk patients:** Intervention 1: £276 Intervention 2: £306 Intervention 3 : £230 **Low risk patients:** Intervention 1: £177 Intervention 2: £217	**QALYs (mean per patient):** **High risk patients:** Intervention 1: 12.755 Intervention 2: 12.758 Intervention 3 : 12.764 **Intermediate risk patients:** Intervention 1: 12.765 Intervention 2: 12.767 Intervention 3 : 12.769 **Low risk patients:** Intervention 1: 12.769 Intervention 2: 12.769	**ICER:** **High risk patients:** Intervention 1: Dominated Intervention 2: Dominated Intervention 3: Dominant 95% CI: NR Probability Intervention 1 cost-effective (£20K/30K threshold): 4%/4% Probability Intervention 2 cost-effective (£20K/30K threshold): 18%/18% Probability Intervention 3 cost-effective (£20K/30K threshold): 78%/79% **Intermediate risk patients:** Intervention 1: Dominated

The relative effectiveness of the interventions was based on a systematic review and network meta-analysis (NMA) of published RCTs. **Perspective:** UK NHS and PSS **Time horizon:** lifetime **Treatment effect duration:**[(a)] 14 days **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	Male: 50% **Intervention 1:** LMWH (which is assumed to be the background pharmacological prophylaxis therapy administered to all patients) for a duration of 7 days (standard duration). **Intervention 2:** Knee-length AES in addition to pharmacological prophylaxis (LMWH) for a duration of 7 days (standard duration). **Intervention 3:** Thigh-length AES in addition to pharmacological prophylaxis (LMWH) for a duration of 7 days (standard duration).	Intervention 3 : £182 **Currency & cost year:** 2014 UK pounds **Cost components incorporated:** Prophylaxis costs. Monitoring tests. Nurse time. VTE treatment costs. Costs of treating adverse events , long term consequences and complications (CTEPH, PTS, bleeding, stroke, re-operation)	Intervention 3 : 12.771	Intervention 2: Dominated Intervention 3: Dominant 95% CI: NR Probability Intervention 1 cost-effective (£20K/30K threshold): 5%/4% Probability Intervention 2 cost-effective (£20K/30K threshold): 18%/18% Probability Intervention 3 cost-effective (£20K/30K threshold): 78%/78% **Low risk patients:** Intervention 1: comparator Intervention 2: Dominated Intervention 3: £2,632 95% CI: NR Probability Intervention 1 cost-effective (£20K/30K threshold): 9%/7% Probability Intervention 2 cost-effective (£20K/30K threshold): 18%/18% Probability Intervention 3 cost-effective (£20K/30K threshold): 74%/75% **Analysis of uncertainty:** Probabilistic sensitivity analysis was conducted. Analyses were reported for two main scenarios : i- the base-case NMA based on the no interaction, random-effects analysis, using the predictive distribution output ii- the direct meta-analysis comparing thigh-length AES (plus pharmacological prophylaxis) with

				knee-length AES (plus pharmacological prophylaxis). Additionally, sensitivity analysis changing the price used for AES (based on published prices and clinical experts estimate) and the level of patient adherence to thigh-length stockings (90% and 75%). The results of all scenario and sensitivity analyses were largely consistent with the base case results.
Data sources				
Health outcomes: baseline event rates were based on the ACCP 2012 guideline, which used systematic review of RCTs published between 2003 and 2010 and meta-analysis. LMWH was considered the baseline treatment. The relative treatment effect was based on a systematic review and NMA of RCT data. long-term events included are PTS, CTEPH, stroke, VTE recurrence, The main health outcomes included were DVT (symptomatic), DVT (asymptomatic), PE (symptomatic) and major bleeding. **Quality-of-life weights:** from published sources largely using the EQ-5D UK tariff. **Cost sources:** standard UK unit cost sources including NHS reference costs and the drug tariff in addition to data from published sources and clinical expert opinions.				
Comments				
Source of funding: NIHR HTA. **Limitations:** Mixed population of all surgery types, however subgroup analysis is also presented. The model did not include some relevant health outcomes; e.g. clinically-relevant non-major bleeding, minor bleeding and surgical site infection.				
Overall applicability:[(b)]Directly applicable **Overall quality**[(c)] Potentially serious limitations				

Abbreviations: AES: anti-embolism stockings; 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NMA: network-meta-analysis; NR: not reported; pa: probabilistic analysis; PTS: post-thrombotic syndrome; QALYs: quality-adjusted life years; RCT: randomised controlled trial; TKR: total knee replacement; THR: total hip replacement.

a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

b) Directly applicable / Partially applicable / Not applicable

c) Minor limitations / Potentially serious limitations / Very serious limitations

J233 Bariatric surgery

Study	[Wade 2015[985]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Systematic review and economic model, including value of information analysis. **Approach to analysis:** a two stage modelling approach, a decision tree for the acute phase (up to 14 days post-surgery) followed by Markov models for the long term phase with annual cycles. The relative effectiveness of the interventions was based on a systematic review and network meta-analysis (NMA) of published RCTs. **Perspective:** UK NHS and PSS **Time horizon:** lifetime **Treatment effect duration:**[(a)] 14 days	**Population:** Patients undergoing any general surgery (subgroups considered were THR, TKR, general surgery for high risk patients, general surgery for medium risk patients and general surgery for low risk patients. The results presented here are for the general surgery subgroup-high risk patients only. **Cohort settings:** Start age: 60 years Male: 50% **Intervention 1:** LMWH (which is assumed to be the background pharmacological prophylaxis therapy administered to all patients) for a duration of 7 days (standard duration). **Intervention 2:** Knee-length AES in addition to pharmacological prophylaxis (LMWH) for a	**Total costs (mean per patient):** **High risk patients:** Intervention 1: £521 Intervention 2: £522 Intervention 3 : £345 **Currency & cost year:** 2014 UK pounds **Cost components incorporated:** Prophylaxis costs. Monitoring tests. Nurse time. VTE treatment costs. Costs of treating adverse events , long term consequences and complications (CTEPH, PTS, bleeding, stroke, re-operation)	**QALYs (mean per patient):** **High risk patients:** Intervention 1: 12.755 Intervention 2: 12.758 Intervention 3 : 12.764	**ICER:** **High risk patients:** Intervention 1: Dominated Intervention 2: Dominated Intervention 3: Dominant 95% CI: NR Probability Intervention 1 cost-effective (£20K/30K threshold): 4%/4% Probability Intervention 2 cost-effective (£20K/30K threshold): 18%/18% Probability Intervention 3 cost-effective (£20K/30K threshold): 78%/79% **Analysis of uncertainty:** Probabilistic sensitivity analysis was conducted. Analyses were reported for two main scenarios : 1. the base-case NMA based on the no interaction, random-effects analysis, using the predictive distribution output 2. the direct meta-analysis comparing thigh-length AES (plus pharmacological prophylaxis) with knee-length AES (plus pharmacological prophylaxis). Additionally, sensitivity analysis changing

Discounting: Costs: 3.5% ; Outcomes: 3.5%	duration of 7 days (standard duration). **Intervention 3:** Thigh-length AES in addition to pharmacological prophylaxis (LMWH) for a duration of 7 days (standard duration).			the price used for AES (based on published prices and clinical experts estimate) and the level of patient adherence to thigh-length stockings (90% and 75%). The results of all scenario and sensitivity analyses were largely consistent with the base case results.
Data sources				
Health outcomes: baseline event rates were based on the ACCP 2012 guideline, which used systematic review of RCTs published between 2003 and 2010 and meta-analysis. LMWH was considered the baseline treatment. The relative treatment effect was based on a systematic review and NMA of RCT data. long-term events included are PTS, CTEPH, stroke, VTE recurrence, The main health outcomes included were DVT (symptomatic), DVT (asymptomatic), PE (symptomatic) and major bleeding. **Quality-of-life weights:** from published sources largely using the EQ-5D UK tariff. **Cost sources:** standard UK unit cost sources including NHS reference costs and the drug tariff in addition to data from published sources and clinical expert opinions.				
Comments				
Source of funding: NIHR HTA. **Limitations:** Mixed population of all surgery types, however subgroup analysis is also presented. The model did not include some relevant health outcomes; e.g. clinically-relevant non-major bleeding, minor bleeding and surgical site infection.				
Overall applicability:[(b)]Directly applicable **Overall quality**[(c)] Potentially serious limitations				

Abbreviations: AES: anti-embolism stockings; 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NMA: network-meta-analysis; NR: not reported; pa: probabilistic analysis; PTS: post-thrombotic syndrome; QALYs: quality-adjusted life years; RCT: randomised controlled trial; TKR: total knee replacement; THR: total hip replacement.

a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

b) Directly applicable / Partially applicable / Not applicable

c) Minor limitations / Potentially serious limitations / Very serious limitations

J34 Cardiac surgery

No relevant health economic studies were identified.

J35 Thoracic surgery

Study	[Wade 2015[985]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Systematic review and economic model, including value of information analysis. **Approach to analysis:** a two stage modelling approach, a decision tree for the acute phase (up to 14 days post-surgery) followed by Markov models for the long term phase with annual cycles. The relative effectiveness of the interventions was based on a systematic review and network meta-analysis (NMA) of published RCTs. **Perspective:** UK NHS and PSS	**Population:** Patients undergoing any general surgery (subgroups considered were THR, TKR, general surgery for high risk patients, general surgery for medium risk patients and general surgery for low risk patients. The results presented here are for the general surgery subgroups – high risk patients only. **Cohort settings:** Start age: 60 years Male: 50% **Intervention 1:** LMWH (which is assumed to be the background pharmacological prophylaxis therapy administered to all patients) for a duration of 7 days (standard duration). **Intervention 2:**	**Total costs (mean per patient):** **High risk patients:** Intervention 1: £521 Intervention 2: £522 Intervention 3 : £345 **Currency & cost year:** 2014 UK pounds **Cost components incorporated:** Prophylaxis costs. Monitoring tests. Nurse time. VTE treatment costs. Costs of treating adverse events , long term consequences and complications (CTEPH, PTS, bleeding, stroke, re-operation)	**QALYs (mean per patient):** **High risk patients:** Intervention 1: 12.755 Intervention 2: 12.758 Intervention 3 : 12.764	**ICER:** **High risk patients:** Intervention 1: Dominated Intervention 2: Dominated Intervention 3: Dominant 95% CI: NR Probability Intervention 1 cost-effective (£20K/30K threshold): 4%/4% Probability Intervention 2 cost-effective (£20K/30K threshold): 18%/18% Probability Intervention 3 cost-effective (£20K/30K threshold): 78%/79% **Analysis of uncertainty:** Probabilistic sensitivity analysis was conducted. Analyses were reported for two main scenarios : iii- the base-case NMA based on the no interaction, random-effects analysis, using the predictive distribution output iv- the direct meta-analysis comparing thigh-length AES (plus

Time horizon: lifetime **Treatment effect duration:**[(a)] 14 days **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	Knee-length AES in addition to pharmacological prophylaxis (LMWH) for a duration of 7 days (standard duration). **Intervention 3:** Thigh-length AES in addition to pharmacological prophylaxis (LMWH) for a duration of 7 days (standard duration).			pharmacological prophylaxis) with knee-length AES (plus pharmacological prophylaxis). Additionally, sensitivity analysis changing the price used for AES (based on published prices and clinical experts estimate) and the level of patient adherence to thigh-length stockings (90% and 75%). The results of all scenario and sensitivity analyses were largely consistent with the base case results.
Data sources				
Health outcomes: baseline event rates were based on the ACCP 2012 guideline, which used systematic review of RCTs published between 2003 and 2010 and meta-analysis. LMWH was considered the baseline treatment. The relative treatment effect was based on a systematic review and NMA of RCT data. long-term events included are PTS, CTEPH, stroke, VTE recurrence, The main health outcomes included were DVT (symptomatic), DVT (asymptomatic), PE (symptomatic) and major bleeding. **Quality-of-life weights:** from published sources largely using the EQ-5D UK tariff. **Cost sources:** standard UK unit cost sources including NHS reference costs and the drug tariff in addition to data from published sources and clinical expert opinions.				
Comments				
Source of funding: NIHR HTA. **Limitations:** Mixed population of all surgery types, however subgroup analysis is also presented. The model did not include some relevant health outcomes; e.g. clinically-relevant non-major bleeding, minor bleeding and surgical site infection.				
Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] Potentially serious limitations				

Abbreviations: AES: anti-embolism stockings; 95% CI: 95% confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NMA: network-meta-analysis; NR: not reported; pa: probabilistic analysis; PTS: post-thrombotic syndrome; QALYs: quality-adjusted life years; RCT: randomised controlled trial; TKR: total knee replacement; THR: total hip replacement.

a) *For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.*
b) *Directly applicable / Partially applicable / Not applicable*
c) *Minor limitations / Potentially serious limitations / Very serious limitations*

J.36 Vascular surgery

No relevant economic studies were identified.

J.37 Head and neck surgery

J.37.1 Oral and maxillofacial surgery

No relevant economic studies were identified.

J.37.2 Ear, nose and throat (ENT) surgery

No relevant economic studies were identified.

Appendix K: GRADE tables

K.1 Risk assessment for people admitted to hospital

K.1.1 Patients admitted to hospital

No relevant clinical studies identified.

K.1.2 Hospital admissions

No relevant clinical studies identified.

K.1.3 Risk assessment tools in patients admitted to hospital

Table 1: Clinical evidence profile: Department of Health risk tool versus no risk tool for general medical patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Department of Health risk tool	No Department of Health risk tool	Relative (95% CI)	Absolute		
Mortality, VTE-related (90 days)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9.0059/100000 (0.009%)	9.8395/100000 (0.010%)	Rate ratio 0.92 (0.39 to 2.15)	0 fewer per 1000 (from 0 fewer to 0 more)	VERY LOW	CRITICAL
Readmission, VTE-related (30 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	124.9600/100000 (0.13%)	126.5443/100000 (0.13%)	Rate ratio 0.99 (0.82 to 1.19)	0 fewer per 1000 (from 0 fewer to 0	VERY LOW	IMPORTANT

										more)		
Readmission, VTE-related (90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	193.9492/100000 (0.19%)	189.6753/100000 (0.19%)	Rate ratio 1.02 (0.88 to 1.19)	0 fewer per 1000 (from 0 fewer to 0 more)	VERY LOW	IMPORTANT
VTE (symptomatic or asymptomatic) (up to 90 days from hospital discharge) – no data reported DVT (symptomatic or asymptomatic) (up to 90 days from hospital discharge) – no data reported Pulmonary embolism (up to 90 days from hospital discharge) Fatal pulmonary embolism (up to 90 days from hospital discharge) – no data reported Major bleeding (up to 90 days from hospital discharge) – no data reported Quality of life (validated scores) (up to 90 days from hospital discharge) – no data reported												

[1] 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

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

Table 2: Department of Health risk tool: achieving >90% of admissions assessed using Department of Health risk tool versus achieving <90% assessed using risk tool for general medical patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Department of Health risk tool**	**No Department of Health risk tool**	**Relative (95% CI)**	**Absolute**		
Mortality, VTE-related post-discharge (non-surgical admissions) – length of stay >3 days (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1135/2590547 (0.04%)	-	RR 0.96 (0.81 to 1.14)	-	LOW	CRITICAL
Mortality, VTE-related post-discharge (non-surgical admissions) – length of stay <4 days (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	761/10719502 (0.007%)	-	RR 0.74 (0.6 to 0.92)	-	VERY LOW	CRITICAL
Mortality, primary VTE-related post-discharge (non-surgical admissions) –length of stay >3 days (follow-up 90 days)												

1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	669/2590547 (0.03%)	-	RR 0.89 (0.71 to 1.1)	-	VERY LOW	CRITICAL
Mortality, primary VTE-related post-discharge (non-surgical admissions) – length of stay <4 days (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	450/10719502 (0.004%)	-	RR 0.62 (0.47 to 0.81)	-	VERY LOW	CRITICAL
DVT (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/1323 (2.3%)	4/1569 (0.25%)	RR 0.95 (0.83 to 1.09)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
PE (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/1323 (0.53%)	17/1569 (1.1%)	RR 0.79 (0.67 to 0.94)	2 fewer per 1000 (from 1 fewer to 4 fewer)	VERY LOW	CRITICAL
VTE (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	236/302057 (0.08%)	189/302057 (0.06%)	RR 0.88 (0.79 to 0.98)	0 fewer per 1000 (from 0 fewer to 0 fewer)	LOW	CRITICAL
Fatal pulmonary embolism (up to 90 days from hospital discharge) – no data reported Major bleeding (up to 90 days from hospital discharge) – no data reported Quality of life (validated scores) (up to 90 days from hospital discharge) – no data reported												

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

Table 3: Padua prediction score versus no risk tool for general medical patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Padua prediction score versus no risk tool	Control	Relative (95% CI)	Absolute		
DVT												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/235 (8.5%)	61/393 (15.5%)	RR 0.55 (0.34 to 0.88)	70 fewer per 1000 (from 19 fewer to 102	⊕OOO VERY	CRITICAL

										fewer)	LOW	
PE												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/235 (0.43%)	0/393 (0%)	OR 14.47 (0.25 to 830.93)	-[3]	⊕OOO VERY LOW	CRITICAL
Fatal PE												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/235 (0.43%)	0/393 (0%)	OR 14.47 (0.25 to 830.93)	-[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding												
1	observational studies	very serious[1]	no serious inconsistency		very serious[2]	none	0/235 (0%)	2/393 (0.51%)	OR 0.2 (0.01 to 3.55)	4 fewer per 1000 (from 5 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
All cause mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/235 (1.7%)	6/393 (1.5%)	RR 1.11 (0.32 to 3.91)	2 more per 1000 (from 10 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effects could not be calculated due to zero events in control arm

Table 4: Caprini risk tool versus no risk tool for surgical patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Caprini risk tool**	**No Caprini risk tool**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up 30 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/1569 (0.25%)	30/1323 (2.3%)	RR 0.11 (0.04 to 0.32)	20 fewer per 1000 (from 15 fewer to 22 fewer)	VERY LOW	CRITICAL
PE (follow-up 30 days)												

1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/1323 (0.53%)	17/1569 (1.1%)	RR 0.49 (0.2 to 1.17)	6 fewer per 1000 (from 9 fewer to 2 more)	VERY LOW	CRITICAL
All-cause mortality (up to 90 days from hospital discharge) – no data reported VTE (symptomatic or asymptomatic) (up to 90 days from hospital discharge) – no data reported Fatal pulmonary embolism (up to 90 days from hospital discharge) – no data reported Major bleeding (up to 90 days from hospital discharge) – no data reported Quality of life (validated scores) (up to 90 days from hospital discharge) – no data reported												

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

Table 5: Department of Health risk tool: achieving >90% of admissions assessed using Department of Health risk tool versus achieving <90% assessed using risk tool for surgical patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Department of Health risk tool**	**No Department of Health risk tool**	**Relative (95% CI)**	**Absolute**		
VTE-related mortality post-discharge (surgical admissions) - >3 days (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	516/1550794 (0.03%)	-	RR 0.73 (0.46 to 1.16)	-	VERY LOW	CRITICAL
VTE-related mortality post-discharge (surgical admissions) - <4 days (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	113/2851838 (0.004%)	-	RR 0.82 (0.65 to 1.03)	-	VERY LOW	CRITICAL
Primary VTE-related mortality post-discharge (surgical admissions) - >3 days (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	226/1550794 (0.01%)	-	RR 0.62 (0.44 to 0.89)	-	VERY LOW	CRITICAL
Primary VTE-related mortality post-discharge (surgical admissions) - <4 days (follow-up 90 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	62/2851838 (0.002%)	-	RR 0.57 (0.3 to 1.06)	-	VERY LOW	CRITICAL

VTE (symptomatic or asymptomatic) (up to 90 days from hospital discharge) – no data reported
DVT (symptomatic or asymptomatic) (up to 90 days from hospital discharge) – no data reported
Pulmonary embolism (up to 90 days from hospital discharge) – no data reported
Fatal pulmonary embolism (up to 90 days from hospital discharge) – no data reported
Major bleeding (up to 90 days from hospital discharge) – no data reported
Quality of life (validated scores) (up to 90 days from hospital discharge) – no data reported

[1] 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

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

K.2 Risk assessment for people having day procedures

K.2.1 VTE day procedures

No relevant clinical studies identified.

K.2.2 Major bleeding day procedures

No relevant clinical studies identified.

K.2.3 Risk assessment tools in patients who are having day procedures (including surgery and chemotherapy) at hospital

No relevant clinical studies identified.

K.3 Reassessment

K.3.1 Reassessment of people who are admitted to hospital

No relevant clinical studies identified.

K.3.2 Reassessment of people who are having day procedures at hospital

No relevant clinical studies identified.

K.4 Risk assessment for pregnant women and women up to 6 weeks postpartum

No relevant clinical studies identified.

K.5 Giving information to patients and planning for discharge

No relevant clinical studies identified.

K.6 General VTE prevention for everyone in hospital

None.

K.7 Nursing care: Early mobilisation and hydration

None.

K.8 Obesity

No relevant clinical studies identified.

K.9 People using antiplatelets

No relevant clinical studies identified.

K.10 People using anticoagulation therapy

Table 6: Clinical evidence profile: LMWH versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH versus UFH	Control	Relative (95% CI)	Absolute		
Mortality (90 days) (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/84 (0%)	0%	OR 0 (-0.02 to 0.02)	0 fewer per 1000 (from 20 more to 20 more)[2]	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding (90 days) (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/84 (0%)	4/93 (4.3%)	OR 0.14 (0.02 to 1.04)	37 fewer per 1000 (from 42 fewer to 2 more)	⊕⊕OO LOW	CRITICAL

[1] 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
[2] Calculated manually in RevMan
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

K.11 Acute coronary syndromes

No relevant clinical studies identified.

K.12 Acute stroke patients

Table 7: Clinical evidence profile: AES (above knee) versus no prophylaxis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AES (above-knee)**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
Mortality, all cause (follow-up mean 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	131/1321 (9.9%)	114/1294 (8.8%)	RR 1.11 (0.88 to 1.42)	10 more per 1000 (from 11 fewer to 37 more)	LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up mean 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	212/1321 (16%)	231/1294 (17.9%)	RR 0.9 (0.76 to 1.07)	18 fewer per 1000 (from 43 fewer to 12 more)	MODERATE	CRITICAL
PE (follow-up mean 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/1321 (0.98%)	20/1294 (1.5%)	RR 0.65 (0.33 to 1.31)	5 fewer per 1000 (from 10 fewer to 5 more)	VERY LOW	CRITICAL
PE, fatal (follow-up mean 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/1256 (0.08%)	1/1262 (0.08%)	OR 1.00 (0.06 to 16.07)	0 fewer per 1000 (from 1 fewer to 12 more)	VERY LOW	CRITICAL
Mechanical complications - skin breaks (follow-up mean 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/1256 (5.1%)	16/1262 (1.3%)	RR 4.02 (2.34 to 6.91)	38 more per 1000 (from 17 more to 75 more)	MODERATE	IMPORTANT
Mechanical complications - foot ischaemia (follow-up mean 30 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/1256 (0.56%)	2/1262 (0.16%)	RR 3.52 (0.73 to 16.9)	4 more per 1000 (from 0 fewer to 25 more)	VERY LOW	IMPORTANT

- Major bleeding (up to 45 days from hospital discharge) – not reported

[1] 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

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

Table 8: Clinical evidence profile: AES (thigh length) versus AES (knee length)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AES (thigh-length)**	**AES (knee-length)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	182/1552 (11.7%)	174/1562 (11.1%)	RR 1.05 (0.87 to 1.28)	6 more per 1000 (from 14 fewer to 31 more)	MODERATE	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up mean 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	177/1552 (11.4%)	211/1562 (13.5%)	RR 0.84 (0.7 to 1.02)	22 fewer per 1000 (from 41 fewer to 3 more)	LOW	CRITICAL
PE (follow-up mean 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/1552 (1.5%)	75/1562 (4.8%)	RR 0.31 (0.19 to 0.49)	33 fewer per 1000 (from 24 fewer to 39 fewer)	MODERATE	CRITICAL
Mechanical complications - discontinued due to skin concerns (follow-up mean 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	61/1552 (3.9%)	75/1562 (4.8%)	RR 0.82 (0.59 to 1.14)	9 fewer per 1000 (from 20 fewer to 7 more)	LOW	IMPORTANT

Mechanical complications - discontinued due to discomfort (follow-up mean 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	127/1552 (8.2%)	77/1562 (4.9%)	RR 1.66 (1.26 to 2.18)	33 more per 1000 (from 13 more to 58 more)	MODERATE	IMPORTANT
• Major bleeding (up to 45 days from hospital discharge) – not reported • Fatal PE (up to 90 days from hospital discharge) – not reported												

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

[2] 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 9: Clinical evidence profile: IPCD (full leg) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD (full-leg)**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	156/1438 (10.8%)	189/1438 (13.1%)	RR 0.83 (0.68 to 1.01)	22 fewer per 1000 (from 42 fewer to 1 more)	LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up mean 30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	239/1451 (16.5%)	310/1451 (21.4%)	RR 0.77 (0.66 to 0.90)	49 fewer per 1000 (from 21 fewer to 73 fewer)	LOW	CRITICAL
PE (follow-up mean 30 days)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	29/1438 (2%)	35/1438 (2.4%)	RR 0.83 (0.51 to 1.35)	4 fewer per 1000 (from 11 fewer to 8 more)	VERY LOW	CRITICAL
Mechanical complications - skin breaks (follow-up mean 30 days)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/1438 (3.1%)	20/1438 (1.4%)	RR 2.2 (1.3 to 3.71)	17 more per 1000 (from 4 more to 38 more)	LOW	IMPORTANT
• Major bleeding (up to 45 days from hospital discharge) – not reported • Fatal PE (up to 90 days from hospital discharge) – not reported												

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

Table 10: Clinical evidence profile: IPCD + AES versus UFH + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD + AES**	**UFH + AES**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 22 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/117 (0%)	0/120 (0%)	Not estimable3	0 fewer per 1000 (from 20 fewer to 20 more)3	MODERATE	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up mean 22 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/117 (6.8%)	5/120 (4.2%)	RR 1.64 (0.55 to 4.87)	27 more per 1000 (from 19 fewer to 161 more)	VERY LOW	CRITICAL
• Pulmonary embolism (7- 90 days from hospital discharge) – not reported • Major bleeding (up to 45 days from hospital discharge) – not reported • Fatal PE (up to 90 days from hospital discharge) – not reported												

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Zero events in both arms. Risk difference calculated in Review Manager.

Table 11: Clinical evidence profile: IPCD + AES versus AES

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD + AES**	**AES**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 22 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/191 (7.9%)	24/192 (12.5%)	RR 0.65 (0.37 to 1.14)	44 fewer per 1000 (from 79 fewer to 17 more)	LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up mean 22 days)												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	11/181 (6.1%)	17/184 (9.2%)	RR 0.65 (0.15 to 2.79)	32 fewer per 1000 (from 79 fewer to 165 more)	VERY LOW	CRITICAL
• Pulmonary embolism (7- 90 days from hospital discharge) – not reported • Major bleeding (up to 45 days from hospital discharge) – not reported • Fatal PE (up to 90 days from hospital discharge) – not reported												

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment I^2 over 50% and sub-groups do not explain herterogeneity. Analysed using random effects model.

Table 12: Clinical evidence profile: UFH + AES versus AES

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH + AES**	**AES**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 22 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/120 (0%)	0/115 (0%)	Not estimable3	0 fewer per 1000 (from 20 fewer to 20 more)3	MODERATE	CRITICAL
DVT (symptomatic or asymptomatic) (follow-up mean 22 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/120 (4.2%)	6/115 (5.2%)	RR 0.8 (0.25 to 2.54)	10 fewer per 1000 (from 39 fewer to 80 more)	VERY LOW	CRITICAL

- Pulmonary embolism (7- 90 days from hospital discharge) – not reported
- Major bleeding (up to 45 days from hospital discharge) – not reported
- Fatal PE (up to 90 days from hospital discharge) – not reported

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Zero events in both arms. Risk difference calculated in Review Manager.

Table 13: Clinical evidence profile: UFH versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 28 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/160 (21.3%)	58/177 (32.8%)	RR 0.65 (0.45 to 0.94)	115 fewer per 1000 (from 20 fewer to 180 fewer)	LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up mean 28 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/195 (17.4%)	132/207 (63.8%)	RR 0.29 (0.21 to 0.40)	453 fewer per 1000 (from 383 fewer to 504 fewer)	MODERATE	CRITICAL

- Pulmonary embolism (7- 90 days from hospital discharge) – not reported
- Major bleeding (up to 45 days from hospital discharge) – not reported
- Fatal PE (up to 90 days from hospital discharge) – not reported

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

338 **Table 14: Clinical evidence profile: LMWH (standard dose; standard duration) versus no prophylaxis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH	No prophylaxis	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 14 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/82 (17.1%)	5/81 (6.2%)	RR 2.63 (1.02 to 6.81)	101 more per 1000 (from 1 more to 359 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic or asymptomatic) (follow-up 14 days)												
2	randomised trials	serious[1]	serious[3]	no serious indirectness	very serious	none	21/69 (30.4%)	32/80 (40%)	RR 0.72 (0.31 to 1.66)	112 fewer per 1000 (from 276 fewer to 264 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	1/30 (3.3%)	2/30 (6.7%)	RR 0.50 (0.05 to 5.22)	33 fewer per 1000 (from 63 fewer to 281 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/52 (0%)	0/51 (0%)	Not estimable[5]	0 fewer per 1000 (from 40 fewer to 40 more)[5]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/52 (0%)	1/51 (2%)	OR 0.13 (0.00 to 6.69)	17 fewer per 1000 (from 20 fewer to 98 more)	⊕OOO VERY LOW	IMPORTANT
Haemorrhagic transformation (follow-up 15 days)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/50 (8%)	3/52 (5.8%)	RR 1.39 (0.33 to 5.89)	22 more per 1000 (from 39 fewer to 282 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] I2 over 50% and sub-groups do not explain heterogeneity. Downgraded for inconsistency and analysed using random effects.
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[5] Relative effect could not be calculated as no events occurred in either group

Table 15: Clinical evidence profile: LMWH (standard dose; standard duration) versus aspirin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH**	**Aspirin**	**Relative (95% CI)**	**Absolute**		
Mortality, all-cause (follow-up 90 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	60/507 (11.8%)	58/491 (11.8%)	RR 1.00 (0.71 to 1.41)	0 fewer per 1000 (from 34 fewer to 48 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 15 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/507 (0.59%)	9/491 (1.8%)	RR 0.32 (0.09 to 1.19)	12 fewer per 1000 (from 17 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 15 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/507 (0.79%)	4/491 (0.81%)	RR 0.97 (0.24 to 3.85)	0 fewer per 1000 (from 6 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 15 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/507 (0.39%)	2/491 (0.41%)	RR 0.97 (0.14 to 6.85)	0 fewer per 1000 (from 4 fewer to 24 more)	⊕⊕OO LOW	CRITICAL

Modified Rankin Scale (follow-up 90 days; assessed with: score 0-2) (higher score is worse)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	188/507 (37.1%)	206/491 (42%)	RR 0.88 (0.76 to 1.03)	50 fewer per 1000 (from 101 fewer to 13 more)	⊕⊕OO LOW	IMPORTANT
Barthel Index (follow-up 90 days; assessed with: score 60-100) (higher score is better)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	313/507 (61.7%)	320/491 (65.2%)	RR 0.95 (0.86 to 1.04)	33 fewer per 1000 (from 91 fewer to 26 more)	⊕⊕OO LOW	IMPORTANT
Heparin-induced thrombocytopenia (follow-up mean 90 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/507 (0.39%)	2/491 (0.41%)	RR 0.97 (0.14 to 6.85)	0 fewer per 1000 (from 4 fewer to 24 more)	⊕⊕OO LOW	IMPORTANT
• Fatal PE – not reported												

345 [1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

346 **Table 16: Clinical evidence profile: LMWH (standard dose; standard duration) versus UFH**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH**	**UFH**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 90 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	142/1262 (11.3%)	146/1257 (11.6%)	RR 0.96 (0.77 to 1.19)	5 fewer per 1000 (from 27 fewer to 22 more)	MODERATE	CRITICAL
DVT (symptomatic or asymptomatic) (follow-up mean 14 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	81/742 (10.9%)	142/741 (19.2%)	RR 0.57 (0.44 to 0.73)	82 fewer per 1000 (from 52 fewer to 107 fewer)	MODERATE	CRITICAL
PE (follow-up mean 14 days)												

3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/1044 (0.29%)	11/1048 (1%)	RR 0.33 (0.1 to 1.11)	7 fewer per 1000 (from 9 fewer to 1 more)	LOW	CRITICAL
Major bleeding (follow-up mean 14 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/1255 (1.2%)	11/1251 (0.88%)	RR 1.34 (0.61 to 2.94)	3 more per 1000 (from 3 fewer to 17 more)	VERY LOW	IMPORTANT
PE, fatal (follow-up mean 14 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/1044 (0.19%)	5/1048 (0.48%)	OR 0.42 (0.1 to 1.87)	3 fewer per 1000 (from 4 fewer to 4 more)	VERY LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up mean 14 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	47/983 (4.8%)	54/978 (5.5%)	RR 0.87 (0.59 to 1.27)	7 fewer per 1000 (from 23 fewer to 15 more)	VERY LOW	IMPORTANT
Heparin-induced thrombocytopenia (follow-up unclear)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	1/272 (0.37%)	2/273 (0.73%)	OR 0.51 (0.05 to 4.69)	4 fewer per 1000 (from 7 fewer to 26 more)	VERY LOW	IMPORTANT
Neurological bleeds - haemorrhagic transformation only (follow-up mean 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	1/106 (0.94%)	0/106 (0%)	OR 7.39 (0.15 to 372.38)	-4	VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment because the majority of the evidence had indirect outcomes (includes primary bleeds)
[4] Absolute effects could not be calculated due to zero events in one of the arms.

K.13 Acutely ill medical patients

Table 17: Clinical evidence profile: LMWH (standard dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH	No prophylaxis	Relative (95% CI)	Absolute		
All-cause mortality (follow-up not reported- 110 days)												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	285/3477 (8.2%)	295/3461 (8.5%)	RR 0.97 (0.83 to 1.13)	3 fewer per 1000 (from 14 fewer to 11 more)	LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 110 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	17/272 (6.3%)	42/263 (16%)	RR 0.39 (0.23 to 0.67)	97 fewer per 1000 (from 53 fewer to 123 fewer)	LOW	CRITICAL
PE (symptomatic or asymptomatic) (follow-up not reported - 110 days)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	8/2027 (0.39%)	13/1986 (0.65%)	RR 0.6 (0.25 to 1.45)	3 fewer per 1000 (from 5 fewer to 3 more)	VERY LOW	CRITICAL
Major bleeding (follow-up not reported - 110 days)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	23/2259 (1%)	15/2242 (0.67%)	RR 1.53 (0.80 to 2.92)	4 more per 1000 (from 1 fewer to 13 more)	VERY LOW	CRITICAL
PE, fatal (follow-up not reported - 90 days)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12/2164 (0.55%)	20/2130 (0.94%)	RR 0.58 (0.31 to 1.11)	4 fewer per 1000 (from 6 fewer to 1 more)	VERY LOW	CRITICAL
Heparin-induced thrombocytopenia (follow-up not reported)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/140 (0.71%)	3/140 (2.1%)	RR 0.33 (0.04 to 3.17)	14 fewer per 1000 (from 21 fewer to 46 more)	VERY LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/4171 (0.43%)	14/4136 (0.34%)	RR 1.27 (0.63 to 2.56)	1 more per 1000 (from 1 fewer to 5 more)	VERY LOW	IMPORTANT

354 **Table 18: Clinical evidence profile: LMWH (high dose; standard duration) versus no prophylaxis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (high dose)**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/135 (4.4%)	6/135 (4.4%)	RR 1.00 (0.33 to 3.02)	0 fewer per 1000 (from 30 fewer to 90 more)	VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/132 (3%)	12/131 (9.2%)	RR 0.33 (0.11 to 1.00)	61 fewer per 1000 (from 82 fewer to 0 more)	LOW	CRITICAL
PE, fatal (follow-up 10 days)												
1	randomised trials	serious	no serious inconsistency	no serious indirectness	very serious[2]	none	1/132 (0.76%)	3/131 (2.3%)	RR 0.33 (0.03 to 3.14)	15 fewer per 1000 (from 22 fewer to 49 more)	VERY LOW	CRITICAL

- Pulmonary embolism (7-90 days from hospital discharge) – not reported
- Major bleeding (up to 45 days from hospital discharge) – not reported

355 **Table 19: Clinical evidence profile: LMWH (low dose; standard duration) versus no prophylaxis**

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (low)	No prophylaxis	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 110 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	51/351 (14.5%)	50/362 (13.8%)	RR 1.05 (0.73 to 1.51)	7 more per 1000 (from 37 fewer to 70 more)	VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 110 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	44/263 (16.7%)	42/263 (16%)	RR 1.05 (0.71 to 1.54)	8 more per 1000 (from 46 fewer to 86 more)	VERY LOW	CRITICAL
PE (follow-up 110 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/263 (0.38%)	3/263 (1.1%)	RR 0.33 (0.03 to 3.18)	8 fewer per 1000 (from 11 fewer to 25 more)	VERY LOW	CRITICAL
Major bleeding (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	4/351 (1.1%)	7/362 (1.9%)	RR 0.59 (0.17 to 2)	8 fewer per 1000 (from 16 fewer to 19 more)	VERY LOW	CRITICAL
PE, fatal (follow-up 110 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/263 (0.38%)	1/263 (0.38%)	OR 1.00 (0.06 to 16.03	0 fewer per 1000 (from 4 fewer to 54 more)	VERY LOW	CRITICAL

356 **Table 20: Clinical evidence profile: LMWH (high dose; standard duration) versus LMWH (standard dose; standard duration)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high	LMWH (standard	Relative (95% CI)	Absolute		

							dose)	dose)				
All-cause mortality (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/46 (0%)	1/45 (2.2%)	OR 0.13 (0 to 6.67)	19 fewer per 1000 (from 22 fewer to 109 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/46 (0%)	0/45 (0%)	See comment[2]	0 fewer per 1000 (from 40 fewer to 40 more)[2]	⊕⊕OO LOW	CRITICAL
Heparin-induced thrombocytopenia (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/46 (0%)	0/45 (0%)	See comment[2]	0 fewer per 1000 (from 40 fewer to 40 more)[2]	⊕⊕OO LOW	IMPORTANT

- DVT (symptomatic and asymptomatic) – not reported
- PE – not reported
- Fatal PE – not reported

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

Table 21: Clinical evidence profile: LMWH (standard dose; standard duration) versus LMWH (low dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**LMWH (low dose)**	**Relative (95% CI)**	**Absolute**		

All-cause mortality (follow-up 110 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	41/360 (11.4%)	51/351 (14.5%)	RR 0.78 (0.53 to 1.15)	32 fewer per 1000 (from 68 fewer to 22 more)	VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 110 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	17/272 (6.3%)	44/263 (16.7%)	RR 0.37 (0.22 to 0.64)	105 fewer per 1000 (from 60 fewer to 130 fewer)	LOW	CRITICAL
PE (follow-up 110 days)												
1	randomised trials	serious	no serious inconsistency	serious[2]	very serious[3]	none	0/272 (0%)	1/263 (0.38%)	OR 0.13 (0.00 to 6.59)	3 fewer per 1000 (from 4 fewer to 21 more)	VERY LOW	CRITICAL
Major bleeding (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	6/360 (1.7%)	1/351 (0.28%)	RR 5.85 (0.71 to 48.34)	14 more per 1000 (from 1 fewer to 135 more)	VERY LOW	CRITICAL
PE, fatal (follow-up 110 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/272 (0.74%)	1/263 (0.38%)	OR 1.89 (0.20 to 18.23)	3 more per 1000 (from 3 fewer to 61 more)	VERY LOW	CRITICAL

362 **Table 22: Clinical evidence profile: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (extended duration)**	**LMWH (standard duration)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 90 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	105/2159 (4.9%)	105/2176 (4.8%)	RR 1.01 (0.77 to 1.31)	0 more per 1000 (from 11 fewer to 15 more)	LOW	CRITICAL
PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/1818 (0.17%)	7/1867 (0.37%)	RR 0.44 (0.11 to 1.7)	2 fewer per 1000 (from 3 fewer to 3 more)	VERY LOW	CRITICAL
PE, fatal (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/1818 (0%)	2/1867 (0.11%)	OR 0.14 (0.01 to 2.22)	1 fewer per 1000 (from 1 fewer to 1 more)	VERY LOW	CRITICAL

- Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge) – not reported
- Major bleeding (up to 45 days from hospital discharge) – not reported

363 **Table 23: Clinical evidence profile: LMWH (standard dose; standard duration) + AES versus AES**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH + AES**	**AES**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 90 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	348/4171 (8.3%)	355/4136 (8.6%)	RR 0.97 (0.84 to 1.12)	3 fewer per 1000 (from 14 fewer to 10 more)	HIGH	CRITICAL
Major bleeding (follow-up 8 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	16/4171 (0.38%)	11/4136 (0.27%)	RR 1.44 (0.67 to 3.10)	1 more per 1000 (from 1 fewer to 6 more)	LOW	CRITICAL

Clinically relevant non-major bleeding (follow-up 8 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	18/4171 (0.43%)	14/4136 (0.34%)	RR 1.27 (0.63 to 2.56)	1 more per 1000 (from 1 fewer to 5 more)	LOW	IMPORTANT

- Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge) – not reported
- Pulmonary embolism (7-90 days from hospital discharge) – not reported
- Fatal PE (up to 90 days from hospital discharge) – not reported

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365 **Table 24: Clinical evidence profile: LMWH (standard dose; standard duration) versus UFH**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH**	**UFH**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 8 - 90 days)												
5	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[4]	none	113/3270 (3.5%)	119/3226 (3.7%)	RR 0.93 (0.59 to 1.45)	3 fewer per 1000 (from 15 fewer to 17 more)	VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 8 - 90 days)												
3	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	30/784 (3.8%)	49/755 (6.5%)	RR 0.57 (0.37 to 0.87)	28 fewer per 1000 (from 8 fewer to 41 fewer)	VERY LOW	CRITICAL
PE (follow-up 8 - 90 days)												
5	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	8/3077 (0.26%)	11/2989 (0.37%)	OR 0.73 (0.31 to 1.73)	1 fewer per 1000 (from 3 fewer to 3 more)	VERY LOW	CRITICAL
Major bleeding (follow-up 8 - 90 days)												

5	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	15/3287 (0.46%)	26/3258 (0.8%)	RR 0.64 (0.33 to 1.23)	3 fewer per 1000 (from 5 fewer to 2 more)	VERY LOW	CRITICAL
PE, fatal (follow-up not reported)												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	1/1049 (0.1%)	1/992 (0.1%)	OR 0.92 (0.06 to 14.82)	0 fewer per 1000 (from 1 fewer to 14 more)	VERY LOW	CRITICAL
Heparin-induced thrombocytopenia (follow-up 90 days)												
3	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	1/1831 (0.05%)	4/1835 (0.22%)	OR 0.31 (0.05 to 1.79)	2 fewer per 1000 (from 2 fewer to 2 more)	VERY LOW	CRITICAL

366 **Table 25: Clinical evidence profile: LMWH (standard dose; standard duration) versus apixaban**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH**	**Apixaban**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/3273 (0.09%)	2/3255 (0.06%)	RR 1.49 (0.25 to 8.92)	0 more per 1000 (from 0 fewer to 5 more)	VERY LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/3266 (0.24%)	7/3251 (0.22%)	RR 1.14 (0.41 to 3.13)	0 more per 1000 (from 1 fewer to 5 more)	VERY LOW	CRITICAL
Major bleeding (including fatal bleeding) (30 days) (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/3217 (0.19%)	15/3184 (0.47%)	RR 0.4 (0.15 to 1.02)	3 fewer per 1000 (from 4 fewer to 0 more)	LOW	CRITICAL
Major plus clinically relevant non-major bleeding (follow-up 30 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	67/3217 (2.1%)	85/3184 (2.7%)	RR 0.78 (0.57 to 1.07)	6 fewer per 1000 (from 11 fewer to 2 more)	LOW	CRITICAL

- Deep vein thrombosis (symptomatic and asymptomatic) (7-90 days from hospital discharge) – not reported
- Fatal PE (up to 90 days from hospital discharge) – not reported

367 **Table 26: Clinical evidence profile: Rivaroxaban versus LMWH (standard dose; standard duration)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rivaroxaban	LMWH	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 35 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	159/3096 (5.1%)	153/3169 (4.8%)	RR 1.06 (0.86 to 1.32)	3 more per 1000 (from 7 fewer to 15 more)	MODERATE	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 35 days)												
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[1]	none	116/2967 (3.9%)	148/3057 (4.8%)	RR 0.81 (0.64 to 1.02)	9 fewer per 1000 (from 17 fewer to 1 more)	VERY LOW	CRITICAL
PE (follow-up 35 days)												
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[1]	none	10/2967 (0.34%)	14/3057 (0.46%)	RR 0.74 (0.33 to 1.65)	1 fewer per 1000 (from 3 fewer to 3 more)	VERY LOW	CRITICAL
Major bleeding (follow-up 35 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/3997 (1.1%)	14/4001 (0.35%)	RR 3.07 (1.68 to 5.61)	7 more per 1000 (from 2 more to 16 more)	HIGH	CRITICAL

- Fatal PE (up to 90 days from hospital discharge) – not reported

368 **Table 27: Clinical evidence profile: Fondaparinux versus no prophylaxis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fondaparinux	No prophylaxis	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/425 (3.3%)	25/414 (6%)	RR 0.55 (0.29 to 1.03)	27 fewer per 1000 (from 43 fewer to 2 more)	LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 15 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/321 (5.6%)	29/323 (9%)	RR 0.62 (0.35 to 1.1)	34 fewer per 1000 (from 58 fewer to 9 more)	LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/425 (0.24%)	4/414 (0.97%)	RR 0.24 (0.03 to 2.17)	7 fewer per 1000 (from 9 fewer to 11 more)	VERY LOW	CRITICAL
Major bleeding (follow-up 15 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/425 (0.24%)	1/414 (0.24%)	OR 0.97 (0.06 to 15.60)	0 fewer per 1000 (from 2 fewer to 34 more)	VERY LOW	CRITICAL
PE, fatal (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/425 (0.71%)	7/414 (1.7%)	RR 0.42 (0.11 to 1.6)	10 fewer per 1000 (from 15 fewer to 10 more)	VERY LOW	CRITICAL

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Table 28: Clinical evidence profile: LMWH (standard dose) versus no VTE prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose) versus no prophylaxis	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 6 months)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	88/538 (16.4%)	14.5%	RR 1.04 (0.8 to 1.37)	6 more per 1000 (from 29 fewer to 54 more)	⊕⊕OO LOW	CRITICAL
DVT (follow-up 6 months)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/533 (3.8%)	6.1%	RR 0.6 (0.35 to 1.04)	24 fewer per 1000 (from 40 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 3-6 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/693 (0.72%)	1.7%	RR 0.41 (0.15 to 1.1)	10 fewer per 1000 (from 14 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 3-6 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/698 (3.3%)	1.1%	RR 1.94 (0.98 to 3.84)	10 more per 1000 (from 0 fewer to 31 more)	⊕⊕OO LOW	CRITICAL
Heparin induced thrombocytopenia (follow-up 3-6 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/447 (0%)	0/451 (0%)	-[3]	0 fewer per 1000 (from 10 more to 10 more)[4]	⊕⊕⊕O MODERATE	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Cannot be calculated due to zero events in both arms
[4] Absolute difference calculated manually in RevMan

Table 29: Clinical evidence profile: LMWH (high dose) versus no VTE prophylaxis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (high dose) versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up median 111-113 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	33/769 (4.3%)	4.2%	RR 1.02 (0.57 to 1.83)	1 more per 1000 (from 18 fewer to 35 more)	⊕⊕OO LOW	CRITICAL
DVT (follow-up median 111-113 days)												
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[1]	none	14/496 (2.8%)	4.4%	RR 0.64 (0.3 to 1.35)	16 fewer per 1000 (from 31 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up median 111-113 days)												
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[1]	none	3/496 (0.6%)	1.1%	RR 0.54 (0.11 to 2.68)	5 fewer per 1000 (from 10 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up median 111-113 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	5/496 (1%)	0%	OR 4.72 (0.75 to 29.73)	-[4]	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] 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
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[4] Absolute risk difference cannot be calculated due to zero events in the control arm

Table 30: Clinical evidence profile: LMWH (standard dose) versus aspirin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose) versus aspirin**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up median 20-25 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/385 (0.26%)	0.2%	OR 1 (0.06 to 16.11)	0 fewer per 1000 (from 2 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up median 20-25 months)												

2	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	0/385 (0%)	1.8%	OR 0.14 (0.03 to 0.61)	15 fewer per 1000 (from 7 fewer to 17 fewer)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up median 20-25 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/385 (0%)	0.7%	OR 0.13 (0.01 to 1.3)	6 fewer per 1000 (from 7 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

Table 31: Clinical evidence profile: Apixaban versus no VTE prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Apixaban (all doses) versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 70 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/93 (1.1%)	6.9%	OR 0.09 (0.01 to 1.31)	62 fewer per 1000 (from 68 fewer to 19 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up mean 70 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/93 (0%)	3.5%	OR 0.01 (0 to 1.49)	35 fewer per 1000 (from 35 fewer to 16 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up mean 70 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/93 (2.2%)	3.5%	OR 0.58 (0.04 to 8.53)	14 fewer per 1000 (from 34 fewer to 201 more)	⊕⊕OO LOW	CRITICAL
CRNMB (follow-up mean 70 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[1]	none	4/93 (4.3%)	0%	OR 3.84 (0.37 to 39.51)	-[3]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[3] Absolute risk difference cannot be calculated due to zero events in the control arm

389 **Table 32: Clinical evidence profile: VKA versus no VTE prophylaxis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA versus no prophylaxis	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up mean 199 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	87/152 (57.2%)	62.3%	RR 0.92 (0.77 to 1.1)	50 fewer per 1000 (from 143 fewer to 62 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up mean 199 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/152 (0.66%)	0.6%	OR 1.05 (0.07 to 16.81)	0 more per 1000 (from 6 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up mean 199 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/152 (0.66%)	1.3%	OR 0.53 (0.06 to 5.18)	6 fewer per 1000 (from 12 fewer to 51 more)	⊕OOO VERY LOW	CRITICAL

390 [1] 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
391 [2] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
392 [3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

393

K.15 Patients with central venous catheters

395 **Table 33: Clinical evidence profile: LMWH (standard dose; standard duration) versus no VTE prophylaxis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	no VTE prophylaxis	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 30 - 112 days)												
5	randomised	serious[1]	serious[2]	no serious	very	none	30/751	34/598	RR 0.82 (0.51	10 fewer per 1000	VERY	CRITICAL

	trials			indirectness	serious[3]		(4%)	(5.7%)	to 1.32)	(from 28 fewer to 18 more)	LOW	
DVT (follow-up 30 - 90 days)												
2	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[3]	none	63/268 (23.5%)	87/249 (34.9%)	RR 0.65 (0.5 to 0.85)	122 fewer per 1000 (from 52 fewer to 175 fewer)	VERY LOW	CRITICAL
PE (follow-up 90 - 112 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/432 (0.23%)	1/280 (0.36%)	OR 0.69 (0.04 to 11.98)	1 fewer per 1000 (from 3 fewer to 38 more)	VERY LOW	CRITICAL
PE, fatal (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/191 (0%)	0/194 (0%)	Not estimable[4]	0 fewer per 1000 (from 10 fewer to 10 more)[4]	VERY LOW	CRITICAL
Major bleeding (follow-up 30 - 112)												
5	randomised trials	serious[1]	serious[2]	very serious[5]	very serious[3]	none	2/671 (0.3%)	1/522 (0.19%)	OR 1.14 (0.11 to 12.13)	0 more per 1000 (from 2 fewer to 21 more)	VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Zero events in both arms. Risk difference calculated in Review Manager.
[5] The majority of the evidence had indirect outcomes

Table 34: Clinical evidence profile: LMWH (low dose; standard duration) versus no VTE prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (low dose)**	**no VTE prophylaxis**	**Relative (95% CI)**	**Absolute**		
Major bleeding (follow-up 21 days)												
1	randomised	serious[1]	no serious	no serious	very	none	0/56	0/57	Not	0 fewer per 1000 (from	VERY	CRITICAL

	trials		inconsistency	indirectness	serious[2]		(0%)	(0%)	estimable[3]	30 fewer to 30 more)[3]	LOW	
Clinically relevant non-major bleeding (follow-up 21 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/56 (0%)	0/57 (0%)	Not estimable[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	VERY LOW	IMPORTANT
Heparin-induced thrombocytopenia (follow-up 21 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/56 (0%)	0/57 (0%)	Not estimable[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	VERY LOW	IMPORTANT
All-cause mortality – no data reported DVT – no data reported PE – no data reported PE, fatal – no data reported												

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

Table 35: Clinical evidence profile: VKA versus no VTE prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VKA**	**no VTE prophylaxis**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	14/114 (12.28%)	11/114 (9.65%)	RR 1.27 (0.6 to 2.68)	26 more per 1000 (from 39 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 30 days)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	25/114 (21.9%)	60/114 (52.6%)	RR 0.39 (0.28 to 0.55)	321 fewer per 1000 (from 237 fewer to 379 fewer)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/114 (0%)	0/114 (0%)	See comment	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Zero events in both arms. Risk difference calculated in Review Manager.

Table 36: Clinical evidence profile: LMWH (standard dose; standard duration) versus VKA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH**	**VKA**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/120 (10%)	14/114 (12.3%)	RR 0.81 (0.39 to 1.68)	23 fewer per 1000 (from 75 fewer to 84 more)	VERY LOW	CRITICAL
DVT (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	48/120 (40%)	25/114 (21.9%)	RR 1.82 (1.21 to 2.75)	180 more per 1000 (from 46 more to 384 more)	VERY LOW	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/120 (0%)	0/114 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	VERY LOW	CRITICAL
PE – no data reported												

PE, fatal – no data reported

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[4] Zero events in both arms. Risk difference calculated in Review Manager.

K.16 Palliative care

No relevant clinical studies identified.

K.17 Critical care

K.17.1 People who are not contraindicated to pharmacological or mechanical prophylaxis

Table 37: Clinical evidence profile: LMWH (standard dose; standard duration) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dalteparin 5000 IU once daily	UFH 5000 IU twice daily	Relative (95% CI)	Absolute		
All-cause mortality (follow-up up to 100 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	698/1873 (37.3%)	763/1873 (40.7%)	RR 0.91 (0.84 to 0.99)	37 fewer per 1000 (from 4 fewer to 65 fewer)	MODERATE	CRITICAL
DVT, any (follow-up at time of death. discharge or at 100 days if patients were still hospitalised)												

1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	138/1873 (7.4%)	161/1873 (8.6%)	RR 0.86 (0.69 to 1.07)	12 fewer per 1000 (from 27 fewer to 6 more)	VERY LOW	CRITICAL
PE (follow-up at time of death. discharge or at 100 days if patients were still hospitalised)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[2]	none	18/1873 (0.96%)	28/1873 (1.5%)	RR 0.64 (0.36 to 1.16)	5 fewer per 1000 (from 10 fewer to 2 more)	MODERATE	CRITICAL
Major bleeding (follow-up at time of death. discharge or at 100 days if patients were still hospitalised)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[2]	none	103/1873 (5.5%)	105/1873 (5.6%)	RR 0.98 (0.75 to 1.28)	1 fewer per 1000 (from 14 fewer to 16 more)	MODERATE	CRITICAL
Heparin-induced thrombocytopenia (follow-up at time of death. discharge or at 100 days if patients were still hospitalised)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[2]	none	5/1873 (0.27%)	12/1873 (0.64%)	RR 0.42 (0.15 to 1.18)	4 fewer per 1000 (from 5 fewer to 1 more)	MODERATE	IMPORTANT
Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

K.172 People who are contraindicated to pharmacological prophylaxis

Table 38: Clinical evidence profile: IPC (half-leg) + AES versus AES alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPC + AES**	**AES only**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 6 days)												
1	randomised	serious[1]	no serious	serious[3]	very	none	10/179	16/183	RR 0.64 (0.3 to	31 fewer per 1000 (from 61	VERY	CRITICAL

	trials		inconsistency		serious[2]		(5.6%)	(8.7%)	1.37)	fewer to 32 more)	LOW	
PE, symptomatic (follow-up 6 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	0/204 (0%)	1/202 (0.5%)	OR 0.13 (0 to 6.75)	4 fewer per 1000 (from 5 fewer to 28 more)	VERY LOW	CRITICAL
Fatal PE (follow-up 6 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/204 (0%)	0/202 (0%)	See comment4	0 fewer per 1000 (from 10 fewer to 10 more)4	LOW	CRITICAL
All-cause mortality – this outcome was reported in the study and was assessed at 90 days. This was not extracted as the study's aim was investigate the short-term effects of using mechanical prophylaxis. After the mechanical prophylaxis was used for 6 days, pharmacological prophylaxis could have been introduced, introducing potential confounding. Major bleeding – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Zero events in both arms. Risk difference calculated in Review Manager.

K.18 Pregnant women and women up to 6 weeks postpartum

Table 39: UFH versus AES (length unspecified)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH versus GCS (undefined)**	**Control**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up discharge from hospital)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/50 (2%)	1/50 (2%)	RR 1 (0.06 to 15.55)	0 fewer per 1000 (from 19 fewer to 291 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 40: UFH versus LMWH (standard dose, standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UFH versus LMWH (standard dose)	Control	Relative (95% CI)	Absolute		
DVT (follow-up discharge from hospital)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/50 (1.8%)	0/50 (0%)	OR 7.39 (0.15 to 372.38)	-	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Risk difference calculated in Review Manager

Table 41: LMWH (low dose, standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (low dose) versus no prophylaxis	Control	Relative (95% CI)	Absolute		
PE (follow-up 42 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/39 (0%)	0/37 (0%)	See comment[3,4]	0 fewer per 1000 (from 50 fewer to 50 more)[3,4]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 42 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/39 (0%)	1/37 (2.7%)	OR 0.13 (0 to 6.47)	23 fewer per 1000 (from 27 fewer to 125 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Could not be calculated as there were no events in the intervention or comparison group
[4] Risk difference calculated in Review Manager

Table 42: LMWH (standard dose, standard duration) versus AES (length unspecified)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH versus AES (length unspecified)**	**Control**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up discharge from hospital)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/50 (0%)	1/50 (2%)	OR 0.14 (0 to 6.82)	17 fewer per 1000 (from 20 fewer to 102 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 43: LMWH (high dose, extended duration) versus LMWH (high dose, standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (ext duration) versus LMWH (st duration)	Control	Relative (95% CI)	Absolute		
PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/335 (0%)	0/311 (0%)	See comment	0 fewer per 1000 (from 10 fewer to 10 more)[4,5]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Could not be calculated as there were no events in the intervention or comparison group
[5] Risk difference calculated in Review Manager

K.19 People with psychiatric illness

No relevant clinical studies identified.

K.20 Anaesthesia

None.

K.21 Lower limb immobilisation

Table 44: Clinical evidence profile: IPCD (below knee) versus no VTE prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPCD (below knee) versus no VTE prophylaxis	Control	Relative (95% CI)	Absolute		
PE (follow-up 41 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/69 (0%)	0/71 (0%)	Not estimable	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 42 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	44/79 (55.7%)	39/83 (47%)	RR 1.19 (0.88 to 1.61)	89 more per 1000 (from 56 fewer to 287 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality – no data Fatal PE – no data Major bleeding – no data												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated manually in RevMan

Table 45: Clinical evidence profile: LMWH (standard prophylactic dose) versus no VTE prophylaxis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose) versus no VTE prophylaxis	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 42 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/188 (0%)	0/189 (0%)	Not estimable	0 fewer per 1000 (from 10 fewer to 10 more)[3]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 38-42 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/287 (0%)	0/295 (0%)	Not estimable	0 fewer per 1000 (from 10 fewer to 10 more)[3]	⊕OOO VERY LOW	CRITICAL
PE (follow-up 38-40 days)												
7	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[2]	none	3/1445 (0.21%)	9/1454 (0.62%)	OR 0.37 (0.12 to 1.14)	4 fewer per 1000 (from 5 fewer to 1 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 38-40 days)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	78/972 (8%)	146/962 (15.2%)	RR 0.53 (0.41 to 0.68)	71 fewer per 1000 (from 49 fewer to 90 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding (follow-up 38-90 days)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/1386 (0.14%)	1/1375 (0.07%)	OR 1.99 (0.21 to 19.23)	1 more per 1000 (from 1 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Heparin-induced thrombocytopenia (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/130 (0.77%)	1/128 (0.78%)	OR 0.98 (0.06 to 15.83)	0 fewer per 1000 (from 7 fewer to 103 more)	⊕OOO VERY LOW	IMPORTANT
Clinically relevant non-major bleeding (follow-up 38 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	1/719 (0.14%)	0/716 (0%)	OR 7.36 (0.15 to	0 more per 1000 (from 2 fewer to 5	⊕OOO VERY LOW	IMPORTANT

									370.84)	more)[3]		

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated manually in Review Manager
[4] Downgraded by 1 or 2 increments due to intervention indirectness because the majority of the evidence was from a study that had mixed standard or high doses of LMWH

Table 46: Clinical evidence profile: Fondaparinux versus LMWH (standard prophylactic dose)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fondaparinux versus LMWH (standard dose)	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 21-45 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/621 (0.16%)	0/622 (0%)	OR 7.4 (0.15 to 372.99)	-	⊕OOO VERY LOW	CRITICAL
PE (follow-up 21-45 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/713 (0.28%)	0/6716 (0%)	OR 7.41 (0.46 to 118.65)	-[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 21-45 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/674 (1.8%)	44/677 (6.5%)	RR 0.27 (0.15 to 0.51)	47 fewer per 1000 (from 32 fewer to 55 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Major bleeding (follow-up 21-45 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/766 (0.13%)	0/762 (0%)	OR 7.35 (0.15 to 370.19)	-[3]	⊕OOO VERY LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 21-45 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/674 (0.15%)	3/670 (0.45%)	OR 0.36 (0.05 to 2.6)	3 fewer per 1000 (from 4 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL
Heparin-induced thrombocytopenia (follow-up 21-45 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/674 (0%)	1/670 (0.15%)	OR 0.13 (0 to 6.78)	1 fewer per 1000 (from 1 fewer to 9 more)	⊕OOO VERY LOW	IMPORTANT
Fatal PE – no data												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effects could not be calculated due to zero events in the control arm

Table 47: Clinical evidence profile: Fondaparinux versus no VTE prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fondaparinux versus no VTE prophylaxis	Control	Relative (95% CI)	Absolute		

PE (follow-up 40 days)												
1	randomised trials	serious	no serious inconsistency	no serious indirectness	very serious[1]	none	0/92 (0%)	2/94 (2.1%)	OR 0.14 (0.01 to 2.2)	18 fewer per 1000 (from 21 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 40 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/92 (1.1%)	11/94 (11.7%)	RR 0.09 (0.01 to 0.71)	106 fewer per 1000 (from 34 fewer to 116 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding (follow-up 40 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/92 (0%)	0/94 (0%)	-	0 fewer per 1000 (from 20 fewer to 20 more)[3]	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] 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
[3] Risk difference calculated manually in Review Manager

K.22 Fragility fractures of the pelvis, hip and proximal femur

Table 48: Clinical evidence profile: LMWH (standard dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 84 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/156 (2.6%)	4/149 (2.7%)	RR 1.17 (0.33 to 4.19)	5 more per 1000 (from 18 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL

DVT (symptomatic and asymptomatic) (follow-up 14 days)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/156 (12.8%)	36/149 (24.2%)	RR 0.59 (0.37 to 0.96)	99 fewer per 1000 (from 10 fewer to 152 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 84 days)											
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/30 (0%)	1/38 (2.6%)	OR 0.17 (0 to 8.65)	22 fewer per 1000 (from 26 fewer to 163 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time-point not reported)											
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/126 (0%)	0/111 (0%)	See comment[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Wound infection (follow-up 84 days)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/30 (6.7%)	2/38 (5.3%)	RR 1.27 (0.19 to 8.47)	14 more per 1000 (from 43 fewer to 393 more)	⊕OOO VERY LOW	IMPORTANT
• Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Zero events in both arms. Risk difference calculated in Review Manager.

Table 49: Clinical evidence profile: LMWH (standard dose; standard duration) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	UFH	Relative (95% CI)	Absolute		

All-cause mortality (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/46 (4.3%)	3/44 (6.8%)	RR 0.64 (0.11 to 3.64)	25 fewer per 1000 (from 61 fewer to 180 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/46 (13%)	0/44 (0%)	OR 7.95 (1.53 to 41.29)	-[4]	⊕⊕⊕O MODERATE	CRITICAL

- DVT (symptomatic and asymptomatic) – not reported
- Major bleeding – not reported
- Fatal PE – not reported

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Absolute effects could not be calculated due to zero events in the control arm

Table 50: Clinical evidence profile: LMWH (standard dose; standard duration) versus fondaparinux

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**Fondaparinux**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 49 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	42/842 (5%)	38/831 (4.6%)	RR 1.09 (0.71 to 1.67)	4 more per 1000 (from 13 fewer to 31 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 11 days)												

1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	117/623 (18.8%)	49/624 (7.9%)	RR 2.39 (1.75 to 3.28)	109 more per 1000 (from 59 more to 179 more)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 11 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/831 (0.12%)	1/840 (0.12%)	RR 1.01 (0.06 to 16.13)	0 more per 1000 (from 1 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 11 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	19/842 (2.3%)	18/831 (2.2%)	RR 1.04 (0.55 to 1.97)	1 more per 1000 (from 10 fewer to 21 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 11 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	2/840 (0.24%)	2/831 (0.24%)	RR 0.99 (0.14 to 7.01)	0 fewer per 1000 (from 2 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] 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 51: Clinical evidence profile: LMWH (standard dose; standard duration) followed by rivaroxaban versus rivaroxaban

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH + rivaroxaban**	**Rivaroxaban**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/96 (1%)	0/96 (0%)	OR 7.39 (0.15 to 372.38)	-[2]	⊕⊕OO LOW	CRITICAL

DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	9/96 (9.4%)	5/96 (5.2%)	RR 1.8 (0.63 to 5.17)	42 more per 1000 (from 19 fewer to 217 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/96 (2.1%)	1/96 (1%)	RR 2 (0.18 to 21.69)	10 more per 1000 (from 9 fewer to 216 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/96 (1%)	0/96 (0%)	OR 7.39 (0.15 to 372.38)	-[2]	⊕⊕OO LOW	CRITICAL
• Major bleeding – not reported												

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Absolute effects could not be calculated due to zero events in one of the arms.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 52: Clinical evidence profile: LMWH (standard dose; standard duration) followed by rivaroxaban versus LMWH (standard dose; extended duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH + rivaroxaban**	**LMWH (extended duration)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[1]	none	1/96 (1%)	1/95 (1.1%)	RR0.99 (0.06 to 15.59)	0 fewer per 1000 (from 10 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL

DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[2]	very serious[1]	none	9/96 (9.4%)	12/95 (12.6%)	RR 0.74 (0.33 to 1.68)	33 fewer per 1000 (from 85 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[1]	none	1/96 (1%)	2/95 (2.1%)	RR 0.49 (0.05 to 5.37)	11 fewer per 1000 (from 20 fewer to 92 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[1]	none	1/96 (1%)	1/95 (1.1%)	RR 0.99 (0.06 to 15.59)	0 fewer per 1000 (from 10 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
• Major bleeding – not reported												

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 53: Clinical evidence profile: LMWH (standard dose; extended duration) versus rivaroxaban

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (extended duration)**	**Rivaroxaban**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	1/95 (1.1%)	0/96 (0%)	OR 7.47 (0.15 to 376.35)	-[2]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 30 days)												

1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[3]	serious[1]	none	12/95 (12.6%)	5/96 (5.2%)	RR 2.43 (0.89 to 6.62)	74 more per 1000 (from 6 fewer to 293 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	2/95 (2.1%)	1/96 (1%)	RR 2.02 (0.19 to 21.92)	11 more per 1000 (from 8 fewer to 218 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	1/95 (1.1%)	0/96 (0%)	OR 7.47 (0.15 to 376.35)	-[2]	⊕OOO VERY LOW	CRITICAL
• Major bleeding – not reported												

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Absolute effects could not be calculated due to zero events in one of the arms.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 54: Clinical evidence profile: Fondaparinux (extended duration) versus fondaparinux (standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fondaparinux (extended duration)**	**Fondaparinux (standard duration)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 25-31 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/327 (1.8%)	8/329 (2.4%)	RR 0.75 (0.26 to 2.15)	6 fewer per 1000 (from 18 fewer to 28 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 25-32 days)												

1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/208 (1.4%)	74/218 (33.9%)	RR 0.04 (0.01 to 0.13)	326 fewer per 1000 (from 295 fewer to 336 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 25-31 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/326 (0%)	2/330 (0.61%)	OR 0.14 (0.01 to 2.19)	5 fewer per 1000 (from 6 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 25-31 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	8/327 (2.4%)	2/329 (0.61%)	RR 4.02 (0.86 to 18.81)	18 more per 1000 (from 1 fewer to 108 more)	⊕⊕⊕O MODERATE	CRITICAL
Fatal PE (follow-up 25-31 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/326 (0%)	1/330 (0.3%)	OR 0.14 (0 to 6.9)	3 fewer per 1000 (from 3 fewer to 18 more)	⊕⊕OO LOW	CRITICAL

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

[2] 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 55: Clinical evidence profile: UFH versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up time-point not reported)												
2	randomised	serious[1]	no serious	serious[2]	serious[3]	none	30/115	17/115	RR 1.76	112 more per 1000 (from 6 more to 297	⊕OOO	CRITICAL

	trials		inconsistency				(26.1%)	(14.8%)	(1.04 to 3.01)	more)	VERY LOW	
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/211 (19.9%)	79/209 (37.8%)	RR 0.53 (0.38 to 0.73)	178 fewer per 1000 (from 102 fewer to 234 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up time-point not reported)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	6/146 (4.1%)	5/144 (3.5%)	RR 1.16 (0.4 to 3.38)	6 more per 1000 (from 21 fewer to 83 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	1/65 (1.5%)	1/65 (1.5%)	OR 1 (0.06 to 16.16)	0 fewer per 1000 (from 14 fewer to 186 more)	⊕OOO VERY LOW	CRITICAL
Wound infection (follow-up time-point not reported)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/75 (12%)	10/75 (13.3%)	RR 0.9 (0.39 to 2.08)	13 fewer per 1000 (from 81 fewer to 144 more)	⊕OOO VERY LOW	IMPORTANT
• Major bleeding – not reported												

[1] 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

[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

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

Table 56: Clinical evidence profile: UFH + AES (length unspecified) versus AES (length unspecified)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH + AES (length unspecified)**	**AES (length unspecified)**	**Relative (95% CI)**	**Absolute**		

All-cause mortality (follow-up time-point not reported)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/29 (0%)	3/23 (13%)	OR 0.1 (0.01 to 0.97)	116 fewer per 1000 (from 3 fewer to 129 fewer)	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 10 days)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/29 (34.5%)	8/23 (34.8%)	RR 0.99 (0.47 to 2.1)	3 fewer per 1000 (from 184 fewer to 383 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up time-point not reported)											
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/29 (6.9%)	1/23 (4.3%)	RR 1.59 (0.15 to 16.42)	26 more per 1000 (from 37 fewer to 670 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time-point not reported)											
1	randomised trials	very serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	0/29 (0%)	0/23 (0%)	See comment[4]	0 fewer per 1000 (from 70 fewer to 70 more)[4]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up time-point not reported)											
1	randomised trials	very serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	0/29 (0%)	1/23 (4.3%)	OR 0.1 (0 to 5.39)	39 fewer per 1000 (from 43 fewer to 153 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Absolute effects could not be calculated due to zero events in the control arm

Table 57: Clinical evidence profile: VKA versus no prophylaxis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA	No prophylaxis	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 90 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/218 (17.9%)	52/218 (23.9%)	RR 0.75 (0.52 to 1.08)	60 fewer per 1000 (from 114 fewer to 19 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 10 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/213 (16.4%)	74/211 (35.1%)	RR 0.47 (0.34 to 0.64)	186 fewer per 1000 (from 126 fewer to 231 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 90 days)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	2/180 (1.1%)	4/180 (2.2%)	OR 0.51 (0.1 to 2.55)	11 fewer per 1000 (from 20 fewer to 33 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time-point not reported)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	19/118 (16.1%)	11/118 (9.3%)	RR 1.73 (0.88 to 3.37)	68 more per 1000 (from 11 fewer to 221 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/100 (1%)	7/100 (7%)	RR 0.14 (0.02 to 1.14)	60 fewer per 1000 (from 69 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Deep wound infection (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	3/38 (7.9%)	4/38 (10.5%)	RR 0.75 (0.18 to 3.13)	26 fewer per 1000 (from 86 fewer to 224 more)	⊕OOO VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

526 **Table 58: Clinical evidence profile: Aspirin (± other prophylaxis) versus no prophylaxis (± other prophylaxis)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	No aspirin	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 35 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	447/6679 (6.7%)	461/6677 (6.9%)	RR 0.97 (0.85 to 1.1)	2 fewer per 1000 (from 10 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 35 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[1]	none	28/6679 (0.42%)	38/6677 (0.57%)	RR 0.74 (0.45 to 1.2)	1 fewer per 1000 (from 3 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 35 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	18/6679 (0.27%)	43/6677 (0.64%)	RR 0.42 (0.24 to 0.72)	4 fewer per 1000 (from 2 fewer to 5 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Wound infection (follow-up 35 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[1]	none	98/6679 (1.5%)	84/6677 (1.3%)	RR 1.17 (0.87 to 1.56)	2 more per 1000 (from 2 fewer to 7 more)	⊕⊕OO LOW	IMPORTANT

- DVT (symptomatic and asymptomatic) – not reported
- Major bleeding – not reported

527 [1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
528 [2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

529 **Table 59: Clinical evidence profile: IPCD versus no prophylaxis**

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPCD	No prophylaxis	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up mean 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/145 (0%)	9/159 (5.7%)	OR 0.14 (0.04 to 0.53)	48 fewer per 1000 (from 26 fewer to 54 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 5-10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/145 (1.4%)	6/159 (3.8%)	RR 0.37 (0.07 to 1.78)	24 fewer per 1000 (from 35 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported • Fatal PE – not reported												

[1] 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

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

K.23 Elective hip replacement

Table 60: Clinical evidence profile: LMWH (standard dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LWMH (standard dose)	No prophylaxis	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 90 days)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/207 (20.3%)	75/184 (40.8%)	RR 0.46 (0.33 to 0.63)	220 fewer per 1000 (from 151 fewer to 273 fewer)	⊕⊕OO LOW	CRITICAL

Major bleeding (follow-up 11-12 days)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/457 (3.1%)	1/457 (0.22%)	OR 5.92 (2.13 to 16.46)	11 more per 1000 (from 2 more to 33 more)	⊕⊕OO LOW	CRITICAL
Wound haematoma (follow-up 10-12 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/161 (22.4%)	21/158 (13.3%)	RR 1.65 (1.06 to 2.59)	86 more per 1000 (from 8 more to 211 more)	⊕⊕OO LOW	IMPORTANT
PE (follow-up 90 days)												
3	randomised trials	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision[2]	none	3/207 (1.4%)	8/184 (4.3%)	RR 0.15 (0.04 to 0.58)	37 fewer per 1000 (from 18 fewer to 42 fewer)	⊕OOO VERY LOW	CRITICAL
Wound infection (follow-up timepoint not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/58 (3.4%)	0/54 (0%)	OR 7.02 (0.43 to 113.83)	-[4]	⊕OOO VERY LOW	IMPORTANT
All-cause mortality – no data reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Absolute effects could not be calculated due to zero events in the control arm

Table 61: Clinical evidence profile: LMWH (standard dose; standard duration) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard	UFH	Relative (95% CI)	Absolute		

							dose)					
All-cause mortality (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/136 (0%)	2/142 (1.4%)	OR 0.14 (0.01 to 2.25)	12 fewer per 1000 (from 14 fewer to 17 more)	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 7-14 days)												
4	randomised trials	serious[1]	serious[3]	serious[4]	serious[2]	none	63/398 (15.8%)	77/386 (19.9%)	RR 0.74 (0.42 to 1.30)	52 fewer per 1000 (from 116 fewer to 60 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 7 days)												
4	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[2]	none	2/474 (0.42%)	8/467 (1.7%)	OR 0.30 (0.09 to 1.04)	12 fewer per 1000 (from 16 fewer to 1 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 7 days)												
3	randomised trials	serious[1]	serious[3]	serious[4]	very serious[2]	none	6/390 (1.5%)	18/384 (4.7%)	OR 0.36 (0.16 to 0.82)	29 fewer per 1000 (from 8 fewer to 39 fewer)	⊕OOO VERY LOW	CRITICAL
Wound haematoma > 5 cm (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/67 (3%)	7/68 (10.3%)	RR 0.29 (0.06 to 1.35)	73 fewer per 1000 (from 97 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
• Fatal PE – not reported												

[1] 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

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

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

[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

545 **Table 62: Clinical evidence profile: LMWH (standard dose; standard duration) versus VKA**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	VKA	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 9 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/190 (25.8%)	28/192 (14.6%)	RR 1.77 (1.16 to 2.69)	112 more per 1000 (from 23 more to 246 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 9 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/271 (2.2%)	4/279 (1.4%)	RR 1.54 (0.44 to 5.41)	8 more per 1000 (from 8 fewer to 63 more)	⊕OOO VERY LOW	CRITICAL
Wound haematoma (follow-up 9 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/271 (2.6%)	2/279 (0.72%)	RR 1.77 (1.16 to 2.69)	6 more per 1000 (from 1 more to 12 more)	⊕OOO VERY LOW	IMPORTANT

- All-cause mortality – not reported
- PE – not reported
- Fatal PE – not reported

546 [1] 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
547 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

548

549 **Table 63: Clinical evidence profile: LMWH (standard dose; standard duration) versus dabigatran**

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	Dabigatran	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 35 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/992 (0.1%)	0/1001 (0%)	OR 7.46 (0.15 to 375.79)	-[2]	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 35 days)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	124/1680 (7.4%)	105/1671 (6.3%)	RR 1.18 (0.92 to 1.51)	11 more per 1000 (from 5 fewer to 32 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 35 days)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/1889 (0.26%)	6/1881 (0.32%)	RR 0.82 (0.25 to 2.69)	1 fewer per 1000 (from 2 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (28-35 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	27/2157 (1.3%)	37/2156 (1.7%)	RR 0.73 (0.45 to 1.19)	5 fewer per 1000 (from 9 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinically relevant non-major bleeding (28-35 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	20/1003 (2%)	23/1010 (2.3%)	RR 0.88 (0.48 to 1.58)	3 fewer per 1000 (from 12 fewer to 13 more)	⊕⊕OO LOW	IMPORTANT

- Fatal PE – not reported

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

[2] Absolute effects could not be calculated due to zero events in the control arm

[3] 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

553 **Table 64: Clinical evidence profile: LMWH (standard dose; standard duration) versus apixaban**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	Apixaban	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 32-38 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/2699 (0.04%)	3/2708 (0.11%)	OR 0.37 (0.05 to 2.62)	1 fewer per 1000 (from 1 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 32-38 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/1911 (3.6%)	22/1944 (1.1%)	RR 3.14 (1.95 to 5.06)	24 more per 1000 (from 11 more to 46 more)	⊕⊕⊕⊕ HIGH	CRITICAL
PE (follow-up 32-38 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/2699 (0.19%)	3/2708 (0.11%)	RR 1.67 (0.4 to 6.99)	1 more per 1000 (from 1 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 32-38 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	18/2659 (0.68%)	22/2673 (0.82%)	RR 0.82 (0.44 to 1.53)	1 fewer per 1000 (from 5 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 32-38 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/2699 (0%)	1/2708 (0.04%)	OR 0.14 (0 to 6.84)	0 fewer per 1000 (from 0 fewer to 2 more)	⊕⊕OO LOW	CRITICAL

Clinically relevant non-major bleeding (follow-up 32-38 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	120/2659 (4.5%)	109/2673 (4.1%)	RR 1.11 (0.86 to 1.43)	4 more per 1000 (from 6 fewer to 18 more)	⊕⊕⊕O MODERATE	IMPORTANT
Heparin-induced thrombocytopenia (follow-up 32-38 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/2659 (0.11%)	2/2673 (0.07%)	RR 1.51 (0.25 to 9.02)	0 more per 1000 (from 1 fewer to 6 more)	⊕⊕OO LOW	IMPORTANT

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

Table 65: Clinical evidence profile: LMWH (standard dose; standard duration) versus rivaroxaban

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard duration)**	**Rivaroxaban**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30-42 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	81/869 (9.3%)	17/864 (2%)	RR 4.74 (2.83 to 7.92)	74 more per 1000 (from 36 more to 136 more)	⊕⊕⊕O MODERATE	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 30-42 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/869 (8.2%)	14/864 (1.6%)	RR 5.04 (2.86 to 8.87)	65 more per 1000 (from 30 more to 128 more)	⊕⊕⊕O MODERATE	CRITICAL

PE (follow-up 30-42 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/869 (0.46%)	1/864 (0.12%)	OR 3.31 (0.57 to 19.15)	3 more per 1000 (from 0 fewer to 21 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 41 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19/1257 (1.5%)	23/1252 (1.8%)	RR 0.82 (0.45 to 1.50)	3 fewer per 1000 (from 10 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 41 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	33/1229 (2.7%)	40/1228 (3.3%)	RR 0.82 (0.52 to 1.3)	6 fewer per 1000 (from 16 fewer to 10 more)	⊕OOO VERY LOW	IMPORTANT
Wound infection (follow-up 41 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/1229 (0.49%)	8/1228 (0.65%)	RR 0.75 (0.26 to 2.15)	2 fewer per 1000 (from 5 fewer to 7 more)	⊕⊕OO LOW	IMPORTANT
• Fatal PE – not reported												

[1] 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

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

[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 66: Clinical evidence profile: LMWH (standard dose; standard duration) versus IPCD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**IPCD**	**Relative (95% CI)**	**Absolute**		

DVT (symptomatic and asymptomatic) (follow-up 84 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/190 (4.2%)	8/196 (4.1%)	RR 1.03 (0.4 to 2.69)	1 more per 1000 (from 24 fewer to 69 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 84 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/196 (1%)	2/194 (1%)	RR 0.99 (0.14 to 6.96)	0 fewer per 1000 (from 9 fewer to 61 more)	⊕⊕OO LOW	CRITICAL
• All-cause mortality – not reported • Fatal PE – not reported												

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
3 Absolute effects could not be calculated due to zero events in the control arm

Table 67: Clinical evidence profile: LMWH (standard dose; standard duration) + AES versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH + AES**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 8-12 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/32 (25%)	13/14 (92.9%)	RR 0.27 (0.15 to 0.5)	678 fewer per 1000 (from 464 fewer to 789 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
PE (follow-up 8-12 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious [1]	none	2/32 (6.3%)	5/14 (35.7%)	RR 0.17 (0.04 to 0.80)	296 fewer per 1000 (from 71 fewer to 343 fewer)	⊕⊕⊕O MODERATE	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported												

• Fatal PE – not reported												

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

Table 68: Clinical evidence profile: LMWH (standard dose; standard duration) + AES versus AES alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH + AES	AES	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 90 days)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/78 (0%)	0/75 (0%)	Not estimable[2]	0 fewer per 1000 (from 30 fewer to 30 more)[2]	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
3	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[4]	none	60/236 (25.4%)	97/239 (40.6%)	RR 0.63 (0.48 to 0.82)	154 fewer per 1000 (from 28 fewer to 235 fewer)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 90 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/236 (0.85%)	2/239 (0.84%)	OR 1.02 (0.14 to 7.30)	0 more per 1000 (from 7 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
• Fatal PE – not reported												

[1] 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
[2] Zero events in both arms. Risk difference calculated in Review Manager.
[3] Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 69: Clinical evidence profile: LMWH (standard dose; standard duration) + AES versus LMWH (standard dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH + AES	LMWH	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 8-12 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/32 (25%)	12/32 (37.5%)	RR 0.67 (0.32 to 1.41)	124 fewer per 1000 (from 255 fewer to 154 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 8-12 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/32 (6.3%)	3/32 (9.4%)	RR 0.67 (0.12 to 3.73)	31 fewer per 1000 (from 83 fewer to 256 more)	⊕⊕OO LOW	CRITICAL

- All-cause mortality – not reported
- Major bleeding – not reported
- Fatal PE – not reported

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

Table 70: Clinical evidence profile: LMWH (standard dose; standard duration) + AES versus fondaparinux + AES

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH + AES	Fondaparinux + AES	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/1133 (0.35%)	2/1140 (0.18%)	RR 2.01 (0.37 to 10.96)	2 more per 1000 (from 1 fewer to 17 more)	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 49 days)												
1	randomised	serious[1]	no serious	no serious	very	none	83/918	36/908	RR 2.28 (1.56	51 more per 1000 (from	⊕OOO VERY	CRITICAL

	trials		inconsistency	indirectness	serious[2]		(9%)	(4%)	to 3.34)	22 more to 93 more)	LOW	
PE (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/1123 (0.27%)	3/1129 (0.27%)	OR 1.01 (0.2 to 4.99)	0 more per 1000 (from 2 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/1123 (0.09%)	0/1129 (0.09%)	OR 1.01 (0.06 to 16.08)	0 fewer per 1000 (from 1 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	32/1133 (2.8%)	47/1140 (4.1%)	RR 0.69 (0.44 to 1.07)	13 fewer per 1000 (from 23 fewer to 3 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 71: Clinical evidence profile: LMWH + IPCD + AES versus IPCD+ AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH + IPCD + AES**	**IPCD + AES**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 11 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/83 (6%)	6/83 (7.2%)	RR 0.83 (0.26 to 2.62)	12 fewer per 1000 (from 53 fewer to 117 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 11 days)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/83 (0%)	0/83 (0%)	Not estimable[2]	0 fewer per 1000 (from 20 fewer to 20 more)[2]	⊕⊕OO LOW	CRITICAL
• All-cause mortality – not reported • Fatal PE – not reported												

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

Table 72: Clinical evidence profile: LMWH (standard dose; standard duration) versus fondaparinux

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	***LMWH (standard dose) versus fondaparinux**	**Control**	**Relative (95% CI)**	**Absolute**		
Major bleeding (follow-up 11-49 days)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32/1216 (2.6%)	47/1224 (3.8%)	RR 0.69 (0.44 to 1.07)	12 fewer per 1000 (from 22 fewer to 3 more)	⊕OOO VERY LOW	CRITICAL
Wound haematoma (follow-up 11 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	3/83 (3.6%)	3/84 (3.6%)	RR 1.01 (0.21 to 4.87)	0 more per 1000 (from 28 fewer to 138 more)	⊕⊕OO LOW	IMPORTANT

[1] 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
[2] The majority of the evidence was based on indirect comparisons.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

587 **Table 73: Clinical evidence profile: LMWH + IPCD + AES versus fondaparinux + IPCD + AES**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH + IPCD + AES	Fondaparinux + IPCD + AES	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 11 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/83 (6%)	6/84 (7.1%)	RR 0.84 (0.27 to 2.66)	11 fewer per 1000 (from 52 fewer to 119 more)	⊕⊕OO LOW	CRITICAL
PE (11 days) (follow-up 11 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/83 (0%)	0/84 (0%)	Not estimable[3]	0 fewer per 1000 (from 20 fewer to 20 more)[2]	⊕⊕OO LOW	CRITICAL
• All-cause mortality – not reported • Fatal PE – not reported												

588 [1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
589 [2] Zero events in both arms. Risk difference calculated in Review Manager.

590 **Table 74: Clinical evidence profile: LMWH (standard dose; standard duration) versus foot pump**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	Foot pump	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 90 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/138 (13%)	24/136 (17.6%)	RR 0.74 (0.42 to 1.3)	46 fewer per 1000 (from 102 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/138 (0%)	1/136 (0.74%)	OR 0.13 (0 to 6.72)	6 fewer per 1000 (from 7 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/138 (0%)	0/136 (0%)	Not estimable[3]	0 fewer per 1000 (from 10 fewer to 10 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported												

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

Table 75: Clinical evidence profile: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (extended duration)**	**LMWH (standard duration)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 27-29 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/90 (0%)	0/89 (0%)	Not estimable[1]	0 fewer per 1000 (from 20 fewer to 20 more)[1]	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 23-35 days)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/350 (7.4%)	68/328 (20.7%)	RR 0.36 (0.23 to 0.55)	133 fewer per 1000 (from 93 fewer to	⊕⊕⊕O	CRITICAL

										160 fewer)	MODERATE	
PE (follow-up 23-35 days)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/382 (0%)	1/368 (0.27%)	OR 0.12 (0.00 to 6.19)	2 fewer per 1000 (from 3 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 23-35 days)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/454 (0%)	1/441 (0.23%)	OR 0.14 (0.00 to 6.87)	2 fewer per 1000 (from 2 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Heparin-induced thrombocytopenia (follow-up 27-29 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	3/224 (1.3%)	2/211 (0.95%)	RR 1.41 (0.24 to 8.37)	4 more per 1000 (from 7 fewer to 70 more)	⊕⊕OO LOW	IMPORTANT
Wound haematoma (follow-up 27-29 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/90 (1.1%)	1/89 (1.1%)	OR 0.99 (0.06 to 15.93)	0 fewer per 1000 (from 11 fewer to 142 more)	⊕⊕OO LOW	IMPORTANT
• Fatal PE – not reported												

[1] Zero events in both arms. Risk difference calculated in Review Manager.

[2] 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

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

Table 76: Clinical evidence profile: LMWH (standard dose; extended duration) + AES versus LMWH (standard dose; standard duration) + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (extended duration) + AES	LMWH (standard duration) + AES	Relative (95% CI)	Absolute		

DVT (symptomatic and asymptomatic) (follow-up 35 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/114 (19.3%)	33/104 (31.7%)	RR 0.61 (0.38 to 0.97)	124 fewer per 1000 (from 10 fewer to 197 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 35 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/111 (0%)	3/106 (2.8%)	OR 0.13 (0.01 to 1.23)	25 fewer per 1000 (from 28 fewer to 6 more)	⊕⊕OO LOW	CRITICAL

- All-cause mortality – not reported
- Major bleeding – not reported
- Fatal PE – not reported

[1] 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

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

Table 77: Clinical evidence profile: LMWH (standard dose; extended duration) versus rivaroxaban

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (extended duration)**	**Rivaroxaban**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 70 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/1558 (0%)	1/1595 (0.06%)	OR 0.14 (0 to 6.98)	1 fewer per 1000 (from 1 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up mean 36 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/1558 (3.4%)	12/1595 (0.75%)	RR 4.52 (2.43 to 8.43)	26 more per 1000 (from 11 more to 56 more)	⊕⊕⊕O MODERATE	CRITICAL

PE (follow-up mean 36 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/1558 (0.06%)	4/1595 (0.25%)	OR 0.31 (0.05 to 1.78)	2 fewer per 1000 (from 2 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up mean 36 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	33/2275 (1.5%)	40/2266 (1.8%)	RR 0.82 (0.52 to 1.30)	3 fewer per 1000 (from 8 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up mean 36 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54/2224 (2.4%)	65/2209 (2.9%)	RR 0.83 (0.58 to 1.18)	5 fewer per 1000 (from 12 fewer to 5 more)	⊕⊕OO LOW	IMPORTANT
Wound infection (follow-up mean 36 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/2224 (0.36%)	8/2209 (0.36%)	RR 0.99 (0.37 to 2.64)	0 fewer per 1000 (from 2 fewer to 6 more)	⊕OOO VERY LOW	IMPORTANT
• Fatal PE – not reported												

[1] 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

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

Table 78: Clinical evidence profile: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration) followed by aspirin (extended duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (extended duration)	Aspirin (extended duration)	Relative (95% CI)	Absolute		

All-cause mortality (follow-up 90 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/400 (0.25%)	0/385 (0%)	OR 7.12 (0.14 to 358.94)	-[2]	⊕⊕OO LOW	CRITICAL
PE (follow-up 90 days)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	3/398 (0.75%)	0/380 (0%)	OR 7.1 (0.74 to 68.48)	-[2]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 90 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/400 (0%)	0/385 (0%)	Not estimable[4]	0 fewer per 1000 (from 0 fewer to 0 more)-[4]	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 90 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/400 (0.25%)	0/385 (0%)	OR 7.12 (0.14 to 358.94)	-	⊕⊕OO LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 90 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/400 (1%)	2/385 (0.52%)	Not estimable[4]	5 more per 1000 (from 3 fewer to 41 more)	⊕⊕OO LOW	IMPORTANT
Wound infection (90 days) (follow-up 90 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/400 (2.5%)	12/385 (3.1%)	RR 0.8 (0.35 to 1.83)	6 fewer per 1000 (from 20 fewer to 26 more)	⊕⊕OO LOW	IMPORTANT

- All-cause mortality – not reported
- DVT (symptomatic and asymptomatic) – not reported
- Major bleeding – not reported

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Absolute effects could not be calculated due to zero events in one of the arms
[3] 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
[4] Zero events in both arms. Risk difference calculated in Review Manager.

Table 79: Clinical evidence profile: LMWH (high dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LWMH (high dose)	No prophylaxis	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 11 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/37 (10.8%)	20/39 (51.3%)	RR 0.21 (0.08 to 0.56)	405 fewer per 1000 (from 226 fewer to 472 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 11 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	0/50 (0%)	0/50 (0%)	Not estimable[3]	0 fewer per 1000 (from 40 fewer to 40 more)[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 11 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/50 (2%)	2/50 (4%)	OR 0.51 (0.05 to 4.98)	19 fewer per 1000 (from 38 fewer to 132 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Zero events in both arms. Risk difference calculated in Review Manager.
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

616 **Table 80: Clinical evidence profile: LMWH (high dose; standard duration) versus UFH**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose)	UFH	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/136 (5.1%)	2/142 (1.4%)	RR 3.65 (0.77 to 17.28)	37 more per 1000 (from 3 fewer to 229 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 10-14 days)												
3	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	67/495 (13.5%)	106/521 (20.3%)	RR 0.57 (0.33 to 0.98)	87 fewer per 1000 (from 4 fewer to 136 fewer)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 10-14 days)												
3	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	2/652 (0.31%)	7/676 (1%)	OR 0.31 (0.05 to 1.81)	7 fewer per 1000 (from 10 fewer to 8 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 10-14 days)												
2	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[2]	none	19/528 (3.6%)	32/541 (5.9%)	RR 0.61 (0.35 to 1.06)	23 fewer per 1000 (from 38 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 10-14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/149 (0.67%)	1/149 (0.67%)	OR 1.00 (0.06 to 16.06)	0 fewer per 1000 (from 6 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Wound haematoma (follow-up 28 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/125 (6.4%)	7/149 (4.7%)	RR 1.36 (0.51 to 3.65)	17 more per 1000 (from 23 fewer to 124 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 81: Clinical evidence profile: LMWH (high dose; standard duration) versus LMWH (standard dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (high dose)**	**LMWH (standard dose)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/136 (0.74%)	0/136 (0%)	OR 7.39 (0.15 to 372.38)	-[4]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 15 days)												
2	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	13/214 (6.1%)	40/286 (14%)	RR 0.45 (0.17 to 1.24)	77 fewer per 1000 (from 116 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/195 (0%)	1/203 (0.49%)	OR 0.14 (0 to 7.1)	4 fewer per 1000 (from 5 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/195 (4.1%)	3/203 (1.5%)	RR 2.78 (0.75 to 10.31)	26 more per 1000 (from 4 fewer to 138 more)	⊕OOO VERY LOW	IMPORTANT

Wound haematoma (follow-up 15 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/50 (12%)	3/50 (6%)	RR 2 (0.53 to 7.56)	60 more per 1000 (from 28 fewer to 394 more)	⊕OOO VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.
[4] Absolute effects could not be calculated due to zero events in the control arm

Table 82: Clinical evidence profile: LMWH (high dose; standard duration) versus fondaparinux

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	***LMWH (high dose) versus fondaparinux**	**Control**	**Relative (95% CI)**	**Absolute**		
Major bleeding (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/1129 (0.97%)	20/1128 (1.8%)	RR 0.55 (0.26 to 1.14)	8 fewer per 1000 (from 13 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
• All-cause mortality – not reported • DVT – not reported • PE – not reported • Fatal PE – not reported												

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

Table 83: Clinical evidence profile: LMWH (high dose; standard duration) + AES versus fondaparinux + AES

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose) + AES	Fondaparinux + AES	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/1129 (0.27%)	6/1128 (0.53%)	RR 0.5 (0.13 to 1.99)	3 fewer per 1000 (from 5 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	65/796 (8.2%)	44/784 (5.6%)	RR 1.46 (1.01 to 2.11)	26 more per 1000 (from 1 more to 62 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/1128 (0%)	5/1126 (0.44%)	OR 0.13 (0.02 to 0.78)	4 fewer per 1000 (from 1 fewer to 4 fewer)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	11/1129 (0.97%)	20/1128 (1.8%)	RR 0.55 (0.26 to 1.14)	8 fewer per 1000 (from 13 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/1128 (0.09%)	0/1126 (0%)	OR 7.38 (0.15 to 371.73)	-[4]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Absolute effects could not be calculated due to zero events in the control arm

636 **Table 84: Clinical evidence profile: LMWH (high dose; standard duration) versus VKA**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose)	VKA	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 43-63 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/1516 (0.59%)	10/1495 (0.67%)	RR 0.89 (0.36 to 2.18)	1 fewer per 1000 (from 4 fewer to 8 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 42-63 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/1516 (0.4%)	9/1495 (0.6%)	RR 0.66 (0.23 to 1.84)	2 fewer per 1000 (from 5 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	6/1516 (0.4%)	4/1495 (0.27%)	RR 1.48 (0.42 to 5.23)	1 more per 1000 (from 2 fewer to 11 more)	⊕OOO VERY LOW	CRITICAL
• DVT (symptomatic and asymptomatic) – not reported • Fatal PE – not reported												

637 [1] 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
638 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
639 [3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

640

641 **Table 85: Clinical evidence profile: LMWH (high dose; extended duration) versus VKA**

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose; extended duration)	VKA	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 42-63 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/643 (0%)	2/636 (0.31%)	RR 0.13 (0.01 to 2.14)	3 fewer per 1000 (from 3 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 42-63 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/643 (2.3%)	20/636 (3.1%)	RR 0.74 (0.38 to 1.44)	8 fewer per 1000 (from 19 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 90 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/2149 (0.28%)	13/2131 (0.61%)	RR 0.48 (0.19 to 1.21)	3 fewer per 1000 (from 5 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 42-63 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	10/643 (1.6%)	37/636 (5.8%)	RR 0.27 (0.13 to 0.53)	42 fewer per 1000 (from 27 fewer to 51 fewer)	⊕⊕OO LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 86: Clinical evidence profile: LMWH (low dose; pre-operation) versus VKA

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (low dose; pre-op)	VKA	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/496 (0.4%)	2/489 (0.41%)	RR 0.99 (0.14 to 6.97)	0 fewer per 1000 (from 4 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 8 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/337 (10.7%)	81/338 (24%)	RR 0.45 (0.31 to 0.64)	132 fewer per 1000 (from 86 fewer to 165 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/496 (0%)	0/489 (0%)	Not estimable[3]	0 fewer per 1000 (from 0 fewer to 0 more)-[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44/496 (8.9%)	22/489 (4.5%)	RR 1.97 (1.2 to 3.24)	44 more per 1000 (from 9 more to 101 more)	⊕⊕OO LOW	CRITICAL
Wound haematomas (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/496 (0.4%)	1/489 (0.2%)	OR 1.92 (0.2 to 18.53)	2 more per 1000 (from 2 fewer to 35 more)	⊕OOO VERY LOW	IMPORTANT

- Fatal PE – not reported

[1] 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

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

[3] Zero events in both arms. Risk difference calculated in Review Manager.

649 **Table 87: Clinical evidence profile: LMWH (low dose; post-operation) versus VKA**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (low dose; post-op)	VKA	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/487 (0%)	2/489 (0.41%)	OR 0.14 (0.01 to 2.17)	4 fewer per 1000 (from 4 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 8 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44/336 (13.1%)	81/338 (24%)	RR 0.55 (0.39 to 0.76)	108 fewer per 1000 (from 58 fewer to 146 fewer)	⊕OOO VERY LOW	CRITICAL
PE (8 days) (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/487 (0%)	0/489 (0%)	Not estimable[3]	0 fewer per 1000 (from 0 fewer to 0 more)-[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32/487 (6.6%)	22/489 (4.5%)	RR 1.46 (0.86 to 2.48)	21 more per 1000 (from 6 fewer to 67 more)	⊕⊕OO LOW	CRITICAL
Wound haematomas (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	2/487 (0.41%)	1/489 (0.2%)	OR 1.96 (0.2 to 18.87)	2 more per 1000 (from 2 fewer to 35 more)	⊕OOO VERY LOW	IMPORTANT

- Fatal PE – not reported

650 [1] 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
651 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
652 [3] Zero events in both arms. Risk difference calculated in Review Manager.

653 **Table 88: Clinical evidence profile: LMWH (low dose; pre-operation) versus LMWH (low dose; post-operation)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (low dose; pre-op)	LMWH (low dose; post-op)	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/496 (0.4%)	0/487 (0%)	OR 7.27 (0.45 to 116.42)	-[3]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 8 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/337 (10.7%)	44/336 (13.1%)	RR 0.82 (0.54 to 1.23)	24 fewer per 1000 (from 60 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/496 (0%)	0/487 (0%)	Not estimable[4]	0 fewer per 1000 (from 0 fewer to 0 more)4	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44/496 (8.9%)	32/487 (6.6%)	RR 1.35 (0.87 to 2.09)	23 more per 1000 (from 9 fewer to 72 more)	⊕⊕OO LOW	CRITICAL
Wound haematomas (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/496 (0.4%)	2/487 (0.41%)	OR 0.98 (0.14 to 6.99)	0 fewer per 1000 (from 4 fewer to 24 more)	⊕OOO VERY LOW	IMPORTANT

• Fatal PE – not reported

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effects could not be calculated due to zero events in the control arm
[4] Zero events in both arms. Risk difference calculated in Review Manager.

Table 89: Clinical evidence profile: LMWH (low dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (low dose)**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
Major bleeding (follow-up 15 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/100 (1%)	0/101 (0%)	OR 7.46 (0.15 to 376.15)[3]	-[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effects could not be calculated due to zero events in one of the arms

Table 90: Clinical evidence profile: LMWH (low dose) + AES versus AES (above-knee)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (low dose) + AES**	**AES (above-knee)**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 8-10 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/93 (31.2%)	44/97 (45.4%)	RR 0.69 (0.47 to 1.00)	141 fewer per 1000 (from 240 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 8-10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/174 (0.57%)	1/183 (0.55%)	OR 1.04 (0.06 to 16.81)	0 more per 1000 (from 5 fewer to 79 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/93 (1.1%)	0/97 (0%)	OR 7.71 (0.15 to 398.09)[3]	-[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effects could not be calculated due to zero events in the control arm

Table 91: Clinical evidence profile: LMWH (low dose; standard duration) + AES versus AES (length unspecified)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (low dose) + AES**	**AES (length unspecified)**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/81 (25.9%)	36/86 (41.9%)	RR 0.62 (0.40 to 0.97)	159 fewer per 1000 (from 13 fewer to 251 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 90 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/81 (0%)	0/86 (0%)	See comment[3]	0 fewer per 1000 (from 20 fewer to 20 more)[3]	⊕OOO VERY LOW	CRITICAL

669 [1] 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
670 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
671 [3] Zero events in both arms. Risk difference calculated in Review Manager.

672 **Table 92: Clinical evidence profile: LMWH (low dose; standard duration) versus LMWH (standard dose; standard duration)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (low dose)**	**LMWH (standard dose)**	**Relative (95% CI)**	**Absolute**		
Major bleeding (Copy) (follow-up 15 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/100 (1%)	2/102 (2%)	OR 0.52 (0.05 to 5.06)	9 fewer per 1000 (from 19 fewer to 72 more)	⊕OOO VERY LOW	CRITICAL

673 [1] 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
674 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

675 **Table 93: Clinical evidence profile: LMWH (low dose; standard duration) + AES versus LMWH (standard dose; standard duration) + AES**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (low dose) + AES**	**LMWH (standard dose) + AES**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 90 days)												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	21/81	27/80	RR 0.77	78 fewer per 1000 (from 176 fewer to 81	⊕⊕OO	CRITICAL

	trials		inconsistency	indirectness			(25.9%)	(33.8%)	(0.48 to 1.24)	more)	LOW	
PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/81 (0%)	1/80 (1.3%)	OR 0.13 (0 to 6.74)	11 fewer per 1000 (from 13 fewer to 66 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported • Fatal PE – not reported												

[1] 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
[2] 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 profile: LMWH (variable dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	***LMWH (variable dose) versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
Major bleeding (follow-up 45 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/100 (0%)	0/100 (0%)	See comment[4]	0 fewer per 1000 (from 20 fewer to 20 more)[5]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] The majority of the evidence was based on indirect comparisons
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Zero events in both arms
[5] Risk difference calculated in Review Manager

Table 95: Clinical evidence profile: LMWH (variable dose; standard duration) + AES versus foot pump + AES

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (variable dose) + AES	Foot pump + AES	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 45 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/94 (6.4%)	3/97 (3.1%)	RR 2.06 (0.53 to 8.01)	33 more per 1000 (from 15 fewer to 217 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 45 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/100 (0%)	0/100 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 45 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/100 (0%)	0/100 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Heparin-induced thrombocytopenia (45 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/100 (1%)	0/100 (0%)	OR 7.39 (0.15 to 372.38)	-[5]	⊕OOO VERY LOW	CRITICAL

- All-cause mortality – not reported

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Zero events in both arms. Risk difference calculated in Review Manager.
[5] Absolute effects could not be calculated due to zero events in control arm

690 **Table 96: Clinical evidence profile: UFH versus no prophylaxis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UFH	No prophylaxis	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up not reported)												
2	randomised trials	serious[1]	serious[4]	serious[2]	serious[3]	none	36/116 (31%)	64/127 (50.4%)	RR 0.62 (0.31 to 1.23)	191 fewer per 1000 (from 348 fewer to 116 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up not reported)												
2	randomised trials	serious[1]	serious[4]	serious[2]	very serious[3]	none	3/83 (3.6%)	0/84 (0%)	OR 7.20 (0.72 to 71.86)5	-5	⊕OOO VERY LOW	CRITICAL
Wound haematomas (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious	no serious imprecision	none	12/68 (17.6%)	1/75 (1.3%)	RR 13.24 (1.77 to 99.12)	74 more per 1000 (from 17 more to 217 more)	⊕⊕OO LOW	IMPORTANT

- All-cause mortality – not reported
- PE – not reported
- Fatal PE – not reported

691 [1] 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
692 [2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
693 [3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
694 [4] Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.
695 [5] Absolute effects could not be calculated due to zero events in control arm

696 **Table 97: Clinical evidence profile: UFH (extended duration) versus UFH (standard duration)**

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH (extended duration)**	**UFH (standard duration)**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 45 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/33 (12.1%)	6/28 (21.4%)	RR 0.57 (0.18 to 1.81)	92 fewer per 1000 (from 176 fewer to 174 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 45 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/33 (0%)	0/33 (0%)	Not estimable	0 fewer per 1000 (from 60 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • PE – not reported • Fatal PE – not reported												

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

Table 98: Clinical evidence profile: UFH versus aspirin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH**	**Aspirin**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/25 (8%)	4/12 (33.3%)	RR 0.24 (0.05 to 1.13)	253 fewer per 1000 (from 317 fewer to 43 more)	⊕⊕OO LOW	CRITICAL

PE (follow-up 7 days)											
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/25 (0%)	1/12 (8.3%)	OR 0.10 (0 to 5.16)	74 fewer per 1000 (from 83 fewer to 236 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 7 days)											
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	1/25 (4%)	1/12 (8.3%)	RR 0.76 (0.05 to 11.39)	20 fewer per 1000 (from 79 fewer to 866 more)	⊕OOO VERY LOW	CRITICAL

- All-cause mortality – not reported
- Major bleeding – not reported

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 99: Clinical evidence profile: UFH + AES (length unspecified) versus AES (length unspecified)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH + AES**	**AES**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up time-point not reported)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/35 (0%)	0/32 (0%)	See comment[3]	0 fewer per 1000 (from 60 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 10 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/32 (25%)	19/28 (67.9%)	RR 0.37 (0.19 to 0.71)	427 fewer per 1000 (from 197 fewer to 550 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

PE (follow-up time-point not reported)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/35 (8.6%)	1/32 (3.1%)	RR 2.74 (0.3 to 25.05)	54 more per 1000 (from 22 fewer to 752 more)	⊕OOO VERY LOW	CRITICAL
• Fatal PE – not reported												

[1] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Zero events in both arms. Risk difference calculated in Review Manager.
[4] 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
[5] Absolute effects could not be calculated due to zero events in one of the arms

Table 100: Clinical evidence profile: Fondaparinux versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	***Fondaparinux versus no pharmacological prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
Major bleeding (follow-up 11-17 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/165 (1.2%)	0/165 (0%)	OR 7.57 (0.47 to 122.16)	-	⊕OOO VERY LOW	CRITICAL
Wound haematoma (follow-up 11 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/84 (3.6%)	1/83 (1.2%)	RR 2.96 (0.31 to 27.92)	24 more per 1000 (from 8 fewer to 324 more)	⊕⊕OO LOW	IMPORTANT
• All-cause mortality – no data reported • DVT– no data reported • PE– no data reported • Fatal PE – no data reported												

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

Table 101: Clinical evidence profile: Fondaparinux + AES versus AES alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fondaparinux + AES	AES alone	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 17 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/81 (0%)	0/82 (0%)	Not estimable[2]	0 fewer per 1000 (from 20 fewer to 20 more)[2]	⊕OOO VERY LOW	CRITICAL
• DVT (symptomatic and asymptomatic) – not reported • PE – not reported • Fatal PE – not reported												

[1] 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
[2] Zero events in both arms. Risk difference calculated in Review Manager.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Absolute effects could not be calculated due to zero events in the control arm

Table 102: Clinical evidence profile: Fondaparinux + IPCD + AES versus IPCD + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fondaparinux + IPCD + AES	IPCD + AES	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 11 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/84 (7.1%)	6/83 (7.2%)	RR 0.99 (0.33 to 2.94)	1 fewer per 1000 (from 48 fewer to 140 more)	⊕⊕OO LOW	CRITICAL

PE (follow-up 11 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/84 (0%)	0/83 (0%)	Not estimable[2]	0 fewer per 1000 (from 20 fewer to 20 more)[3]	⊕⊕OO LOW	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported • Fatal PE – not reported												

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

[2] Zero events in both arms. Risk difference calculated in Review Manager.

Table 103: Clinical evidence profile: Fondaparinux + AES versus fondaparinux

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fondaparinux + AES**	**Fondaparinux**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 35-49 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/391 (0.26%)	3/404 (0.74%)	OR 0.38 (0.05 to 2.7)	5 fewer per 1000 (from 7 fewer to 12 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 35-49 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/391 (0%)	1/404 (0.25%)	OR 0.14 (0 to 7.05)	2 fewer per 1000 (from 2 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 35-49 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/391 (0%)	0/404 (0%)	Not estimable	-[3]	⊕OOO VERY LOW	CRITICAL

Clinically relevant non-major bleeding (follow-up 35-49 days)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/391 (4.1%)	20/404 (5%)	OR 0.14 (0 to 7.05)	42 fewer per 1000 (from 50 fewer to 219 more)	⊕OOO VERY LOW	CRITICAL
• DVT (symptomatic and asymptomatic) – not reported • PE – not reported												

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

Table 104: Clinical evidence profile: Fondaparinux + IPCD + AES versus VKA + IPCD + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fondaparinux + IPCD + AES**	**VKA + IPCD + AES**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/64 (0%)	0/54 (0%)	See comment[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/64 (0%)	0/54 (0%)	See comment[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised	serious[1]	no serious	no serious	very	none	0/64	0/54	See	0 fewer per 1000 (from	⊕OOO VERY	CRITICAL

	trials		inconsistency	indirectness	serious[2]		(0%)	(0%)	comment[3]	30 fewer to 30 more)[3]	LOW	
• Major bleeding – not reported • Fatal PE – not reported												

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

Table 105: Clinical evidence profile: IPCD versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 7-14 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51/195 (26.2%)	102/205 (49.8%)	RR 0.53 (0.4 to 0.69)	234 fewer per 1000 (from 154 fewer to 299 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/152 (0.66%)	1/158 (0.63%)	OR 1.04 (0.06 to 16.7)	0 more per 1000 (from 6 fewer to 90 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported • Fatal PE – not reported												

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

735 **Table 106: Clinical evidence profile: VKA versus no prophylaxis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*VKA versus no prophylaxis	Control	Relative (95% CI)	Absolute		
Major bleeding (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/72 (0%)	0/66 (0%)	See comment[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	Serious[4]	very serious[2]	none	0/45 (0%)	0/50 (0%)	See comment[3]	0 fewer per 1000 (from 40 fewer to 40 more)[3]	⊕OOO VERY LOW	IMPORTANT

- All-cause mortality – not reported
- DVT – not reported
- PE – not reported
- Fatal PE – not reported

736 [1] 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
737 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
738 [3] Zero events in both arms. Risk difference calculated in Review Manager
739 [4] The majority of the evidence was based on indirect comparisons

740 **Table 107: Clinical evidence profile: VKA (extended duration) versus VKA (standard duration)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA (extended duration)	VKA (standard duration)	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 28 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/184 (0%)	0/176 (0%)	Not estimable[2]	0 fewer per 1000 (from 10 fewer to 10 more)[2]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/184 (1.6%)	8/176 (4.5%)	RR 0.36 (0.1 to 1.33)	29 fewer per 1000 (from 41 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/184 (0%)	1/176 (0.57%)	OR 0.13 (0 to 6.52)	5 fewer per 1000 (from 6 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/184 (0.54%)	0/176 (0%)	OR 7.07 (0.14 to 356.89)	-[4]	⊕OOO VERY LOW	CRITICAL

- Fatal PE – not reported

[1] 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
[2] Zero events in both arms. Risk difference calculated in Review Manager.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Absolute effects could not be calculated due to zero events in the control arm.

Table 108: Clinical evidence profile: IPCD versus VKA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD**	**VKA**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 10 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/66 (16.7%)	12/72 (16.7%)	RR 1 (0.47 to 2.11)	0 fewer per 1000 (from 88 fewer to 185 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/66 (0%)	0/72 (0%)	Not estimable[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Fatal PE – not reported												

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

Table 109: Clinical evidence profile: IPCD + AES versus VKA + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD + AES**	**VKA + AES**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 8 days)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	29/148 (19.6%)	44/148 (29.7%)	RR 0.49 (0.13 to 1.83)	152 fewer per 1000 (from 259 fewer to 247 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • PE – not reported • Fatal PE – not reported												

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

[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[5] Zero events in both arms. Risk difference calculated in Review Manager.

Table 110: Clinical evidence profile: Foot pump + AES versus AES alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Foot pump + AES	AES alone	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 6-9 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/39 (10.3%)	16/40 (40%)	RR 0.26 (0.09 to 0.7)	296 fewer per 1000 (from 120 fewer to 364 fewer)	⊕⊕⊕O MODERATE	CRITICAL
• All-cause mortality – not reported • PE – not reported • Major bleeding – not reported • Fatal PE – not reported												

[1] 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 111: Clinical evidence profile: Foot pump + AES versus UFH + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Foot pump + AES	UFH + AES	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 42 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	9/67 (13.4%)	23/65 (35.4%)	RR 0.38 (0.19 to 0.76)	219 fewer per 1000 (from 85 fewer to 287 fewer)	⊕⊕OO LOW	CRITICAL
• All-cause mortality – not reported • PE – not reported												

- Major bleeding – not reported
- Fatal PE – not reported

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

K.24 Elective knee replacement

Table 112: Clinical evidence profile: LMWH (standard dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	No prophylaxis	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/110 (5.5%)	24/189 (21.8%)	RR 0.25 (0.11 to 0.59)	164 fewer per 1000 (from 89 fewer to 194 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/110 (0%)	1/110 (0.91%)	OR 0.14 (0.00 to 6.82)	8 fewer per 1000 (from 9 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 30 days)												
3	randomised trials	serious[1]	serious[6]	serious[4]	very serious[2]	none	4/268 (1.5%)	4/262 (1.5%)	OR 0.98 (0.24 to 3.95)	0 fewer per 1000 (from 12 fewer to 42 more)	⊕OOO VERY LOW	CRITICAL
Wound haematomas (follow-up 8 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/108 (1.9%)	0/111 (0%)	OR 7.67 (0.48 to 123.42)	-[4]	⊕OOO VERY LOW	CRITICAL
Technical complications of mechanical interventions (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/110 (0%)	0/110 (0%)	Not estimable[5]	0 fewer per 1000 (from 20 fewer to 20 more)[5]	⊕OOO VERY LOW	IMPORTANT
Wound infection (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/110 (0%)	2/110 (1.8%)	OR 0.13 (0.01 to 2.16)	16 fewer per 1000 (from 18 fewer to 20 more)	⊕OOO VERY LOW	IMPORTANT
• All-cause mortality – not reported • Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Absolute effects could not be calculated due to zero events in the control arm
[5] Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.
[6] Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.

Table 113: Clinical evidence profile: LMWH (standard dose; standard duration) versus apixaban

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**Apixaban**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 60 days)												
1	randomised	no serious	no serious	no serious	very serious[1]	none	1/1529	3/1528	OR 0.37 (0.05 to	1 fewer per 1000 (from 2 fewer to 3	⊕⊕OO	CRITICAL

	trials	risk of bias	inconsistency	indirectness			(0.07%)	(0.2%)	2.61)	more)	LOW	
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	243/997 (24.4%)	142/971 (14.6%)	RR 1.67 (1.38 to 2.01)	98 more per 1000 (from 56 more to 148 more)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 14 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/1529 (0.07%)	6/1528 (0.39%)	RR 0.17 (0.02 to 1.38)	3 fewer per 1000 (from 4 fewer to 1 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	14/1508 (0.93%)	9/1501 (0.6%)	RR 1.55 (0.67 to 3.57)	3 more per 1000 (from 2 fewer to 15 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/1529 (0%)	1/1528 (0.07%)	OR 0.14 (0 to 6.82)	1 fewer per 1000 (from 1 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	58/1508 (3.8%)	44/1501 (2.9%)	RR 1.31 (0.89 to 1.93)	9 more per 1000 (from 3 fewer to 27 more)	⊕⊕⊕O MODERATE	IMPORTANT
Wound haematoma (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/1508 (0%)	1/1501 (0.07%)	OR 0.13 (0 to 6.79)	1 fewer per 1000 (from 1 fewer to 4 more)	⊕⊕OO LOW	IMPORTANT

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

[2] 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

770 **Table 114: Clinical evidence profile: LMWH (standard dose; standard duration) versus dabigatran**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	Dabigatran	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 13 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/720 (0.14%)	1/730 (0.14%)	OR 1.01 (0.06 to 16.24)	0 more per 1000 (from 1 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 13 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	192/685 (28%)	182/675 (27%)	RR 1.04 (0.87 to 1.24)	11 more per 1000 (from 35 fewer to 65 more)	⊕⊕⊕⊕ HIGH	CRITICAL
PE (follow-up 13 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/730 (0%)	0/720 (0%)	-[2]	-[2]	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 13 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	11/739 (1.5%)	13/724 (1.8%)	RR 0.83 (0.38 to 1.84)	3 fewer per 1000 (from 11 fewer to 15 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 13 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/685 (0.15%)	0/675 (0%)	OR 7.28 (0.14 to 367.03)	-[3]	⊕⊕OO LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 13 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	44/739 (6%)	48/724 (6.6%)	RR 0.9 (0.61 to 1.33)	7 fewer per 1000 (from 26 fewer to 22 more)	⊕⊕OO LOW	IMPORTANT

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

Table 115: Clinical evidence profile: LMWH (standard dose; standard duration) versus rivaroxaban

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	Rivaroxaban	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 35 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/1217 (0.33%)	0/1201 (0%)	OR 7.31 (1.03 to 51.96)	-[3]	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 28 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	174/990 (17.6%)	82/926 (8.9%)	RR 1.99 (1.55 to 2.54)	88 more per 1000 (from 49 more to 136 more)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 17 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/1329 (0.3%)	0/1303 (0%)	OR 7.31 (1.03 to 51.96)	-[3]	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 17 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/1239 (0.48%)	7/1220 (0.57%)	RR 0.84 (0.28 to 2.5)	1 fewer per 1000 (from 4 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 35 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	28/1239 (2.3%)	33/1220 (2.7%)	RR 0.84 (0.51 to 1.37)	4 fewer per 1000 (from 13 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Wound infection (follow-up 17 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/1239 (0.89%)	7/1220 (0.57%)	RR 1.55 (0.6 to 3.98)	3 more per 1000 (from 2 fewer to 17 more)	⊕OOO VERY LOW	CRITICAL
• Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effects could not be calculated due to zero events in the control arm

Table 116: Clinical evidence profile: LMWH (standard dose; standard duration) versus aspirin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**Aspirin**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/112 (12.5%)	18/110 (16.4%)	RR 0.76 (0.4 to 1.46)	39 fewer per 1000 (from 98 fewer to 75 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/112 (0%)	0/110 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported • Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

Table 117: Clinical evidence profile: LMWH (standard dose; standard duration) versus AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	AES	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/110 (5.5%)	14/110 (12.7%)	RR 0.43 (0.17 to 1.07)	73 fewer per 1000 (from 106 fewer to 9 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/110 (0%)	1/110 (0.91%)	OR 0.14 (0 to 6.82)	8 fewer per 1000 (from 9 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Technical complications of mechanical interventions (follow-up time-point not reported)												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	very serious[2]	none	0/110 (0%)	0/110 (0%)	Not estimable[6]	0 fewer per 1000 (from 20 fewer to 20 more)[6]	⊕OOO VERY LOW	IMPORTANT
Wound infection (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/110 (0%)	2/110 (1.8%)	OR 0.13 (0.01 to 2.16)	16 fewer per 1000 (from 18 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported												

- Fatal PE – not reported

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] 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
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[5] Absolute effects could not be calculated due to zero events in the control arm
[6] Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

Table 118: Clinical evidence profile: LMWH (standard dose; standard duration) versus IPCD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	IPCD	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/177 (12.4%)	43/173 (24.9%)	RR 0.49 (0.32 to 0.76)	127 fewer per 1000 (from 60 fewer to 169 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/177 (0%)	0/173 (0%)	Not estimable[3]	0 fewer per 1000 (from 20 fewer to 20 more)[3]	⊕OOO VERY LOW	CRITICAL
Technical complications of mechanical interventions (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/110 (0%)	0/110 (0%)	Not estimable[3]	0 fewer per 1000 (from 20 fewer to 20 more)[3]	⊕OOO VERY LOW	IMPORTANT
Wound infection (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/110 (0%)	1/110 (0.91%)	OR 0.14 (0 to 6.82)	8 fewer per 1000 (from 9 fewer to 50 more)	⊕OOO VERY	IMPORTANT

											LOW	
• All-cause mortality – not reported • Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Zero events in both arms. Risk difference calculated in Review Manager.
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[5] Absolute effects could not be calculated due to zero events in the control arm

Table 119: Clinical evidence profile: LMWH (standard dose; standard duration) versus foot pump + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**Foot pump + AES**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/14 (0%)	4/15 (26.7%)	OR 0.11 (0.01 to 0.91)	228 fewer per 1000 (from 18 fewer to 263 fewer)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up timepoint not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/14 (0%)	1/15 (6.7%)	OR 0.14 (0 to 7.31)	57 fewer per 1000 (from 67 fewer to 276 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • PE – not reported • Major bleeding – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

800 **Table 120: Clinical evidence profile: LMWH (standard dose; standard duration) + AES versus foot pump + AES**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose) + AES	Foot pump + AES	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/89 (53.9%)	57/99 (57.6%)	RR 0.94 (0.73 to 1.21)	35 fewer per 1000 (from 155 fewer to 121 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/89 (0%)	2/99 (2%)	OR 0.15 (0.01 to 2.40)	17 fewer per 1000 (from 20 fewer to 27 more)	⊕OOO VERY LOW	CRITICAL

- All-cause mortality – not reported
- PE – not reported
- Major bleeding – not reported

801 [1] 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
802 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
803 [3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
804 [4] Absolute effects could not be calculated due to zero events in the control arm

805 **Table 121: Clinical evidence profile: LMWH (standard dose; standard duration) versus UFH**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose) + AES	UFH + AES	Relative (95% CI)	Absolute		
Wound haematoma (7-9 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/91 (8.8%)	12/93 (12.9%)	RR 0.68 (0.29 to 1.59)	41 fewer per 1000 (from 92 fewer to 76 more)	⊕OOO VERY LOW	IMPORTANT
• All-cause mortality – not reported • DVT- not reported • PE – not reported • Major bleeding – not reported • Fatal PE – not reported												

[1] 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

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

[3] Zero events in both arms. Risk difference calculated in Review Manager.

Table 122: Clinical evidence profile: LMWH (standard dose; standard duration) + AES versus UFH + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose) + AES	UFH + AES	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (7-9 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/91 (23.1%)	25/93 (26.9%)	RR 0.86 (0.52 to 1.42)	38 fewer per 1000 (from 129 fewer to 113 more)	⊕OOO VERY LOW	CRITICAL
PE (7-9 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/91 (0%)	0/93 (0%)	Not estimable[3]	0 fewer per 1000 (from 20 fewer to 20 more)[3]	⊕OOO VERY LOW	CRITICAL
Wound infection (7-9 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/91 (1.1%)	3/93 (3.2%)	RR 0.34 (0.04 to 3.21)	21 fewer per 1000 (from 31 fewer to 71 more)	⊕OOO VERY LOW	IMPORTANT

- All-cause mortality – not reported
- Major bleeding – not reported
- Fatal PE – not reported

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

Table 123: Clinical evidence profile: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (extended duration)	LMWH (standard duration)	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 27-29 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	33/155 (21.3%)	37/144 (25.7%)	RR 0.83 (0.55 to 1.25)	44 fewer per 1000 (from 116 fewer to 64 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 27-29 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/217 (0%)	2/221 (0.9%)	OR 0.14 (0.01 to 2.20)	8 fewer per 1000 (from 9 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 27-29 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/217 (0%)	1/221 (0.45%)	OR 0.14 (0 to 6.95)	4 fewer per 1000 (from 5 fewer to 26 more)	⊕⊕OO LOW	CRITICAL
Heparin-induced thrombocytopenia (follow-up 27-29 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/217 (0.92%)	2/221 (0.9%)	RR 1.02 (0.14 to	0 more per 1000 (from 8 fewer to 56	⊕⊕OO LOW	IMPORTANT

									7.17)	more)		
• All-cause mortality – not reported • Fatal PE – not reported												

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

Table 124: Clinical evidence profile: LMWH (standard dose; standard duration) + AES versus LMWH (low dose; standard duration) + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose) + AES**	**LMWH (low dose) + AES**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25/74 (33.8%)	34/78 (43.6%)	RR 0.78 (0.52 to 1.16)	96 fewer per 1000 (from 209 fewer to 70 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/74 (1.4%)	1/78 (1.3%)	RR 1.05 (0.07 to 16.55)	1 more per 1000 (from 12 fewer to 199 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported • Fatal PE – not reported												

[1] 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

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

Table 125: Clinical evidence profile: LMWH (standard dose; standard duration) + AES versus AES

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose) + AES	AES	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26/74 (35.1%)	48/79 (60.8%)	RR 0.58 (0.40 to 0.83)	255 fewer per 1000 (from 103 fewer to 365 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/74 (1.4%)	1/79 (1.3%)	OR 1.07 (0.07 to 17.26)	1 more per 1000 (from 12 fewer to 169 more)	⊕OOO VERY LOW	CRITICAL

- All-cause mortality – not reported
- Major bleeding - not reported
- Fatal PE – not reported

[1] 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

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

Table 126: Clinical evidence profile: LMWH (standard dose; standard duration) versus LMWH (low dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	LMWH (low dose)	Relative (95% CI)	Absolute		
Major bleeding (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/91 (1.1%)	0/89 (0%)	OR 7.23 (0.14 to 364.38)	-[3]	⊕OOO VERY LOW	CRITICAL

- All-cause mortality – not reported
- DVT (symptomatic and asymptomatic) – not reported
- PE – not reported
- Fatal PE – not reported

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effects could not be calculated due to zero events in the control arm

Table 127: Clinical evidence profile: LMWH (standard dose; standard duration) + CPM versus CPM

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose) + CPM	CPM	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 6-10 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/25 (0%)	1/25 (4%)	OR 0.14 (0.00 to 6.82)	34 fewer per 1000 (from 40 fewer to 181 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	0/25 (0%)	0/25 (0%)	Not estimable[4]	0 fewer per 1000 (from 70 fewer to 70 more)[4]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/25 (0%)	0/25 (0%)	Not estimable[4]	0 fewer per 1000 (from 70 fewer to 70 more)[4]	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Zero events in both arms. Risk difference calculated in Review Manager.

831 **Table 128: Clinical evidence profile: LMWH (low dose; standard duration) versus no pharmacological prophylaxis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (low dose)	No pharmacological prophylaxis	Relative (95% CI)	Absolute		
Major bleeding (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/89 (0%)	4/89 (4.5%)	OR 0.13 (0.02 to 0.94)	39 fewer per 1000 (from 3 fewer to 44 fewer)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • DVT (symptomatic and asymptomatic) – not reported • PE – not reported • Fatal PE – not reported												

832 [1] 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
833 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

834 **Table 129: Clinical evidence profile: LMWH (low dose; standard duration) + AES versus AES**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (low dose) + AES	AES	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/78 (43.6%)	48/79 (60.8%)	RR 0.72 (0.53 to 0.98)	170 fewer per 1000 (from 12 fewer to 286 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 90 days)												
1	randomised	serious[1]	no serious	no serious	very	none	1/78	1/79	RR 1.01 (0.06	0 more per 1000 (from 12	⊕OOO VERY	CRITICAL

	trials		inconsistency	indirectness	serious[2]		(1.3%)	(1.3%)	to 15.91)	fewer to 189 more)	LOW	

- All-cause mortality – not reported
- Major bleeding – not reported
- Fatal PE – not reported

[1] 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

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

Table 130: Clinical evidence profile: LMWH (high dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose)	No prophylaxis	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/66 (0%)	0/65 (0%)	Not estimable[2]	0 fewer per 1000 (from 30 fewer to 30 more)[2]	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/65 (16.9%)	37/64 (57.8%)	RR 0.29 (0.16 to 0.52)	410 fewer per 1000 (from 278 fewer to 486 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Major bleeding (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/66 (0%)	1/65 (1.5%)	OR 0.13 (0 to 6.72)	13 fewer per 1000 (from 15 fewer to 80 more)	⊕⊕OO LOW	CRITICAL

- PE – not reported
- Fatal PE – not reported

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

[2] Zero events in both arms. Risk difference calculated in Review Manager.

840 **Table 131: Clinical evidence profile: LMWH (high dose; standard duration) versus UFH**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose)	UFH	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 15 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	56/145 (38.6%)	77/143 (53.8%)	RR 0.72 (0.56 to 0.93)	151 fewer per 1000 (from 38 fewer to 237 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 15 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/145 (0%)	1/143 (0.7%)	OR 0.13 (0.00 to 6.73)	6 fewer per 1000 (from 7 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 15 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	3/228 (1.3%)	3/225 (1.3%)	RR 0.99 (0.2 to 4.84)	0 fewer per 1000 (from 11 fewer to 51 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Fatal PE – not reported												

841 [1] 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
842 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
843 [3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

844 **Table 132: Clinical evidence profile: LMWH (high dose; standard duration) versus VKA**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose)	VKA	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 15 days)												
3	randomised	no serious	no serious	no serious	very	none	1/618	3/619	OR 0.37 (0.05	3 fewer per 1000 (from 5	⊕⊕OO	CRITICAL

	trials	risk of bias	inconsistency	indirectness	serious[1]		(0.16%)	(0.48%)	to 2.66)	fewer to 8 more)	LOW	
DVT (symptomatic and asymptomatic) (follow-up 15 days)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	135/488 (27.7%)	217/496 (43.8%)	RR 0.63 (0.53 to 0.75)	162 fewer per 1000 (from 109 fewer to 206 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 15 days)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/488 (0.61%)	4/496 (0.81%)	OR 0.76 (0.17 to 3.37)	2 fewer per 1000 (from 7 fewer to 19 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 15 days)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	16/658 (2.4%)	10/661 (1.5%)	RR 1.61 (0.74 to 3.51)	9 more per 1000 (from 4 fewer to 38 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 12±2 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	0/109 (0%)	0/109 (0%)	Not estimable[3]	0 fewer per 1000 (from 20 fewer to 20 more)[3]	⊕OOO VERY LOW	CRITICAL
Wound haematoma (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/336 (0.3%)	1/334 (0.3%)	RR 0.99 (0.06 to 15.83)	0 fewer per 1000 (from 3 fewer to 44 more)	⊕⊕OO LOW	CRITICAL
Wound infection (follow-up 12±2 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/149 (0.67%)	3/151 (2%)	RR 0.34 (0.04 to 3.21)	13 fewer per 1000 (from 19 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] 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
[3] Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

Table 133: Clinical evidence profile: LMWH (high dose; standard duration) versus fondaparinux

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose)	Fondaparinux	Relative (95% CI)	Absolute		
Major bleeding (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	1/517 (0.19%)	11/517 (2.1%)	RR 0.09 (0.01 to 0.70)	19 fewer per 1000 (from 6 fewer to 21 fewer)	⊕⊕OO LOW	CRITICAL
• All-cause mortality – not reported • DVT (symptomatic and asymptomatic) – not reported • PE – not reported • Fatal PE – not reported												

[1] 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

[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 134: Clinical evidence profile: LMWH (high dose; standard duration) + AES versus fondaparinux + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose) + AES	Fondaparinux + AES	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/517 (0.58%)	2/517 (0.39%)	RR 1.5 (0.25 to 8.94)	2 more per 1000 (from 3 fewer to 31 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	98/361 (27.1%)	45/361 (12.5%)	RR 2.18 (1.58 to 3)	147 more per 1000 (from 72 more to 249 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 49 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/517 (0.77%)	1/517 (0.19%)	RR 4 (0.45 to 35.67)	6 more per 1000 (from 1 fewer to 67 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 49 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/517 (0%)	0/517 (0%)	Not estimable[4]	-[4]	⊕OOO VERY LOW	CRITICAL
• Major bleeding – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Zero events in both arms. Risk difference calculated in Review Manager.

Table 135: Clinical evidence profile: LMWH (high dose; standard duration) versus apixaban

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (high dose)**	**Apixaban**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 60 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/1678 (0.36%)	4/1807 (0.22%)	RR 1.68 (0.48 to 5.79)	2 more per 1000 (from 1 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	107/1231 (8.7%)	110/1350 (8.1%)	RR 1.10 (0.85 to 1.41)	8 more per 1000 (from 12 fewer to 33 more)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 14 days)												
2	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[1]	none	12/1705 (0.7%)	15/1807 (0.83%)	RR 0.87 (0.42 to 1.78)	1 fewer per 1000 (from 5 fewer to 6 more)	⊕⊕OO LOW	CRITICAL

Major bleeding (follow-up 14 days)												
2	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[1]	none	22/1737 (1.3%)	15/1901 (0.79%)	RR 1.63 (0.83 to 3.19)	5 more per 1000 (from 1 fewer to 17 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 14 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/1596 (0%)	2/1599 (0.13%)	OR 0.14 (0.01 to 2.17)	1 fewer per 1000 (from 1 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	47/1588 (3%)	35/1596 (2.2%)	RR 1.35 (0.88 to 2.08)	8 more per 1000 (from 3 fewer to 24 more)	⊕⊕⊕O MODERATE	IMPORTANT
Wound infection (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/149 (0.67%)	6/305 (2%)	RR 0.34 (0.04 to 2.81)	13 fewer per 1000 (from 19 fewer to 36 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis.

Table 136: Clinical evidence profile: LMWH (high dose; standard duration) versus dabigatran

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose)	Dabigatran	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 18 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/868 (0%)	1/857 (0.12%)	OR 0.13 (0 to 6.73)	1 fewer per 1000 (from 1 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL

DVT (symptomatic and asymptomatic) (follow-up 18 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	158/643 (24.6%)	181/604 (30%)	RR 0.82 (0.68 to 0.98)	54 fewer per 1000 (from 6 fewer to 96 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 18 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/643 (0.78%)	6/604 (0.99%)	RR 0.78 (0.24 to 2.55)	2 fewer per 1000 (from 8 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 18 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	12/868 (1.4%)	5/857 (0.58%)	RR 2.37 (0.84 to 6.7)	8 more per 1000 (from 1 fewer to 33 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinically relevant non-major bleeding (follow-up 18 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	21/868 (2.4%)	23/857 (2.7%)	RR 0.9 (0.5 to 1.62)	3 fewer per 1000 (from 13 fewer to 17 more)	⊕⊕OO LOW	IMPORTANT
• Fatal PE – not reported												

[1] 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

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

Table 137: Clinical evidence profile: LMWH (high dose; standard duration) versus rivaroxaban

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (high dose)**	**Rivaroxaban**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 35 days)												
1	randomised	serious[1]	no serious	no serious	very	none	3/1508	4/1526	RR 0.76	1 fewer per 1000	⊕OOO	CRITICAL

	trials		inconsistency	indirectness	serious[1]		(0.2%)	(0.26%)	(0.17 to 3.39)	(from 2 fewer to 6 more)	VERY LOW	
DVT (symptomatic and asymptomatic) (follow-up 17 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	86/959 (9%)	61/965 (6.3%)	RR 1.42 (1.03 to 1.95)	27 more per 1000 (from 2 more to 60 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 17 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	8/1508 (0.53%)	4/1526 (0.26%)	RR 2.02 (0.61 to 6.71)	3 more per 1000 (from 1 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 17 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16/1564 (1%)	27/1584 (1.7%)	RR 0.60 (0.32 to 1.11)	7 fewer per 1000 (from 12 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinically relevant non-major bleeding (follow-up 17 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	30/1508 (2%)	39/1526 (2.6%)	RR 0.78 (0.49 to 1.25)	6 fewer per 1000 (from 13 fewer to 6 more)	⊕⊕OO LOW	CRITICAL
Wound infection (follow-up 17 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	3/1508 (0.2%)	4/1526 (0.26%)	RR 0.76 (0.17 to 3.39)	1 fewer per 1000 (from 2 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL

- Fatal PE – not reported

[1] 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

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

868 **Table 138: Clinical evidence profile: Fondaparinux versus no pharmacological prophylaxis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fondaparinux	No pharmacological prophylaxis	Relative (95% CI)	Absolute		
Major bleeding (follow-up 11-17 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/84 (1.2%)	1/87 (1.1%)	RR 1.04 (0.07 to 16.29)	0 more per 1000 (from 11 fewer to 176 more)	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • DVT – not reported • PE – not reported • Fatal PE – not reported												

869 [1] 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
870 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
871

872 **Table 139: Clinical evidence profile: Fondaparinux + AES versus AES**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fondaparinux + AES	AES	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 11-17 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/158 (0%)	0/161 (0%)	Not estimable	0 fewer per 1000 (from 20 fewer to 20 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 7 days)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/74 (6.8%)	19/74 (25.7%)	RR 0.26 (0.1 to 0.67)	190 fewer per 1000 (from 85 fewer to 231 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
PE (follow-up 7 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/74 (0%)	0/74 (0%)	Not estimable[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕⊕OO LOW	CRITICAL
• Fatal PE – not reported												

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

Table 140: Clinical evidence profile: Fondaparinux + IPCD + AES versus VKA + IPCD + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fondaparinux + IPCD + AES**	**VKA + IPCD + AES**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/54 (0%)	0/64 (0%)	See comment[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/54 (0%)	0/64 (0%)	See comment[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/54 (0%)	0/64 (0%)	See comment[3]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL

- Major bleeding – not reported
- Fatal PE – not reported

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

Table 141: Clinical evidence profile: Apixaban versus VKA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apixaban	VKA	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/208 (0.48%)	0/109 (0%)	OR 4.59 (0.07 to 284.39)	-3	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/208 (10.1%)	29/109 (26.6%)	RR 0.38 (0.23 to 0.63)	165 fewer per 1000 (from 98 fewer to 205 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/208 (0%)	0/109 (0%)	Not estimable4	0 fewer per 1000 (from 10 fewer to 10 more)[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/305 (1.3%)	0/151 (0%)	OR 4.50 (0.56 to 36.39)	-3	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 7 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/208 (0.48%)	0/109 (0%)	OR 4.59 (0.07 to 284.39)	-3	⊕OOO VERY LOW	CRITICAL
Wound infection (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/305 (2%)	3/151 (2%)	RR 0.99 (0.25 to 3.90)	0 fewer per 1000 (from 15 fewer to 58 more)	⊕⊕OO LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effects could not be calculated due to zero events in the control arm
[4] Zero events in both arms. Risk difference calculated in Review Manager.

Table 142: Clinical evidence profile: Dabigatran versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dabigatran**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/129 (0%)	0/124 (0%)	Not estimable[2]	0 fewer per 1000 (from 20 fewer to 20 more)[2]	⊕⊕OO LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/96 (24%)	57/101 (56.4%)	RR 0.42 (0.29 to 0.63)	327 fewer per 1000 (from 209 fewer to 401 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/129 (0%)	0/124 (0%)	Not estimable[2]	0 fewer per 1000 (from 20 fewer to 20 more)[2]	⊕⊕OO LOW	CRITICAL

Major bleeding (follow-up 14 days)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/129 (2.3%)	1/124 (0.81%)	OR 2.64 (0.37 to 19.00)	13 more per 1000 (from 5 fewer to 126 more)	⊕⊕OO LOW	CRITICAL
Clinically relevant non-major bleeding (follow-up 14 days)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/129 (1.6%)	3/124 (2.4%)	RR 0.64 (0.11 to 3.77)	9 fewer per 1000 (from 22 fewer to 67 more)	⊕⊕OO LOW	CRITICAL
• Fatal PE – not reported												

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Zero events in both arms. Risk difference calculated in Review Manager.
[3] 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 143: Clinical evidence profile: Rivaroxaban versus aspirin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivaroxaban**	**Aspirin**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 28 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/102 (2.9%)	18/110 (16.4%)	RR 0.18 (0.05 to 0.59)	134 fewer per 1000 (from 67 fewer to 155 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

PE (follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/102 (0%)	0/110 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported • Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

Table 144: Clinical evidence profile: Foot pump versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Foot pump**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/28 (17.9%)	19/32 (59.4%)	RR 0.3 (0.13 to 0.7)	416 fewer per 1000 (from 178 fewer to 517 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/28 (0%)	0/32 (0%)	Not estimable[4]	0 fewer per 1000 (from 60 fewer to 60 more)[4]	⊕OOO VERY LOW	CRITICAL
• All-cause mortality – not reported • Major bleeding – not reported • Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

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

Table 145: Clinical evidence profile: AES versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES	No prophylaxis	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/110 (12.7%)	24/110 (21.8%)	RR 0.58 (0.32 to 1.07)	92 fewer per 1000 (from 148 fewer to 15 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/110 (0.91%)	1/110 (0.91%)	OR 1.00 (0.06 to 16.09)	0 fewer per 1000 (from 9 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/110 (0%)	0/110 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Technical complications of mechanical interventions (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/110 (0%)	0/110 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	IMPORTANT
Wound infection (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/110 (1.8%)	2/110 (1.8%)	OR 1.00 (0.14 to 6.97)	0 fewer per 1000 (from 16 fewer to 96 more)	⊕OOO VERY	IMPORTANT

											LOW	
• All-cause mortality – not reported • Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Zero events in both arms. Risk difference calculated in Review Manager.

Table 146: Clinical evidence profile: IPCD versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/110 (8.2%)	24/110 (21.8%)	RR 0.38 (0.18 to 0.77)	135 fewer per 1000 (from 50 fewer to 179 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/110 (0%)	1/110 (0.91%)	OR 0.14 (0 to 6.82)	8 fewer per 1000 (from 9 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/110 (0%)	0/110 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Technical complications of mechanical interventions (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/110 (0%)	0/110 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY	IMPORTANT

											LOW	
Wound infection (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/110 (0.91%)	2/110 (1.8%)	OR 0.51 (0.05 to 4.96)	9 fewer per 1000 (from 17 fewer to 66 more)	⊕OOO VERY LOW	IMPORTANT
• All-cause mortality – not reported • Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Zero events in both arms. Risk difference calculated in Review Manager.

Table 147: Clinical evidence profile: IPCD versus AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD**	**AES**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/110 (8.2%)	14/110 (12.7%)	RR 0.64 (0.29 to 1.42)	46 fewer per 1000 (from 90 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/110 (0%)	1/110 (0.91%)	OR 0.14 (0 to 6.82)	8 fewer per 1000 (from 9 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL

Major bleeding (follow-up time-point not reported)											
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/110 (0%)	0/110 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Technical complications of mechanical interventions (follow-up time-point not reported)											
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/110 (0%)	0/110 (0%)	Not estimable[4]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	IMPORTANT
Wound infection (follow-up 30 days)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/110 (0.91%)	2/110 (1.8%)	OR 0.51 (0.05 to 4.96)	9 fewer per 1000 (from 17 fewer to 66 more)	⊕OOO VERY LOW	IMPORTANT

- All-cause mortality – not reported
- Fatal PE – not reported

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Zero events in both arms. Risk difference calculated in Review Manager.

Table 148: Clinical evidence profile: CPM versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CPM**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 90 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/33 (0%)	0/32 (0%)	Not estimable[4]	0 fewer per 1000 (from 60 fewer to 60 more)[4]	⊕OOO VERY LOW	CRITICAL

- All-cause mortality – not reported
- PE – not reported
- Major bleeding – not reported
- Fatal PE – not reported

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Zero events in both arms. Risk difference calculated in Review Manager

K.25 Non-arthroplasty orthopaedic knee surgery

K.25.1 Overall population stratum

Table 149: Clinical evidence profile: LMWH (standard dose, extended duration) versus LMWH (standard dose, standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose, extended duration) versus LMWH (standard dose, standard duration)	Control	Relative (95% CI)	Absolute		
DVT (follow-up 23-28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/72 (2.8%)	28/68 (41.2%)	RR 0.07 (0.02 to 0.27)	383 fewer per 1000 (from 301 fewer to 404 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 23-28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/72 (0%)	0/68 (0%)	See comment	0 fewer per 1000 (from 28 fewer to 28 more)[3]	⊕OOO VERY LOW	CRITICAL

Major bleeding (follow-up 23-28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/72 (0%)	0/68 (0%)	See comment	0 fewer per 1000 (from 28 fewer to 28 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 150: Clinical evidence profile: LMWH (high dose, standard duration) versus AES (full length)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AES (full length) versus LMWH (high dose, standard duration)**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/657 (0%)	0/660 (0%)	See comment	0 fewer per 1000 (from 3 fewer to 3 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/657 (1.5%)	29/660 (4.4%)	RR 0.35 (0.17 to 0.70)	29 fewer per 1000 (from 13 fewer to 36 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/657 (0.3%)	2/660 (0.3%)	OR 1.00 (0.14 to 7.15)	0 fewer per 1000 (from 3 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 8 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/657 (0.3%)	1/660 (0.15%)	OR 1.96 (0.20 to 18.86)	1 more per 1000 (from 1 fewer to 26 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 151: Clinical evidence profile: AES (full length) versus LMWH (high dose, extended duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AES (full length) versus LMWH (high dose, extended duration)**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/444 (0%)	0/660 (0%)	See comment	0 fewer per 1000 (from 4 fewer to 4 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/444 (2%)	29/660 (4.4%)	RR 0.46 (0.22 to 0.97)	24 fewer per 1000 (from 1 fewer to 34 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/444 (0. 45%)	2/660 (0.3%)	See comment	2 more per 1000 (from 2 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/444 (0.23%)	1/660 (0.15%)	OR 1.50 (0.09 to	1 more per 1000 (from 1 fewer to 36	⊕OOO VERY	CRITICAL

									25.41)	more)	LOW	

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 152: Clinical evidence profile: LMWH (high dose, extended duration) versus LMWH (high dose, standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (high dose, extended duration) versus LMWH (high dose, standard duration)**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/444 (0%)	0/657 (0%)	See comment	0 fewer per 1000 (from 4 fewer to 4 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/444 (2%)	10/657 (1.5%)	RR 1.33 (0.55 to 3.25)	5 more per 1000 (from 7 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 8 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/444 (0.45%)	2/657 (0.3%)	OR 1.5 (0.2 to 11.06)	2 more per 1000 (from 2 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/444 (0.23%)	2/657 (0.3%)	OR 0.75 (0.07 to 7.52)	1 fewer per 1000 (from 3 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 153: Clinical evidence profile: Rivaroxaban versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivaroxaban versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/120 (0%)	0/114 (0%)	See comment	0 fewer per 1000 (from 17 fewer to 17 more)[2,3]	⊕⊕OO LOW	CRITICAL
DVT (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/120 (1.7%)	8/114 (7%)	RR 0.24 (0.05 to 1.09)	53 fewer per 1000 (from 67 fewer to 6 more)	⊕⊕⊕O MODERATE	
PE (follow-up 3 months)												
1	randomised	no serious	no serious	no serious	very	none	0/120	0/114	See	0 fewer per 1000	⊕⊕OO	CRITICAL

	trials	risk of bias	inconsistency	indirectness	serious[1]		(0%)	(0%)	comment	(from 17 fewer to 17 more)[2,3]	LOW	
Fatal PE (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/120 (0%)	0/114 (0%)	See comment	0 fewer per 1000 (from 17 fewer to 17 more)[2,3]	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Could not be calculated as there were no events in the intervention or comparison group
[3] Risk difference calculated in Review Manager

K.2.2 Major arthroscopic surgery stratum

Table 154: Clinical evidence profile: LMWH (low dose) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (low dose) versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/117 (0.85%)	5/122 (4.1%)	OR 0.27 (0.05 to 1.35)	30 fewer per 1000 (from 39 fewer to 14 more)	⊕OOO VERY LOW	
PE (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/117 (0%)	0/122 (0%)	-	0 fewer per 1000 (from 16 fewer to 16 more)[4]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 10 days)												
1	randomised	serious[1]	no serious	no serious	very	none	0/117	0/122	Not estimable	0 fewer per 1000	⊕OOO	CRITICAL

	trials		inconsistency	indirectness	serious[2]		(0%)	(0%)		(from 16 fewer to 16 more)[4]	VERY LOW	

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

K.2.5.3 Minor arthroscopic surgery stratum

Table 155: Clinical evidence profile: LMWH (low dose) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (low dose)	No prophylaxis	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/731 (0%)	0/720 (0%)	See comment	0 fewer per 1000 (from 3 fewer to 3 more)[2]	⊕⊕OO LOW	CRITICAL
PE (follow-up 90 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	1/731 (0.14%)	1/720 (0.14%)	OR 0.98 (0.06 to 15.76)	0 fewer per 1000 (from 1 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Risk difference calculated in Review Manager
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

K.2.6 Foot and ankle orthopaedic surgery

No relevant clinical studies were identified.

K.27 Upper limb orthopaedic surgery

No relevant clinical studies were identified.

K.28 Spinal surgery

Table 156: Clinical evidence profile: LMWH (standard dose; standard duration) versus rivaroxaban

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	Rivaroxaban	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/324 (0.31%)	0/341 (0%)	OR 7.79 (0.15 to 392.95)	-[3]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/324 (2.5%)	6/341 (1.8%)	RR 1.4 (0.49 to 4)	7 more per 1000 (from 9 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/324 (0.31%)	1/341 (0.29%)	OR 1.05 (0.07 to 16.88)	0 more per 1000 (from 3 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/324 (0.31%)	2/341 (0.59%)	OR 0.54 (0.06 to 5.2)	3 fewer per 1000 (from 6 fewer to 24	⊕OOO VERY	CRITICAL

										more)	LOW	
Clinically relevant non-major bleeding (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/324 (1.9%)	6/341 (1.8%)	RR 1.05 (0.34 to 3.23)	1 more per 1000 (from 12 fewer to 39 more)	⊕OOO VERY LOW	NOT IMPORTANT
Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effects could not be calculated due to zero events in the control arm

Table 157: Clinical evidence profile: Foot pump + AES (above-knee) versus IPCD (thigh-length/above-knee) + AES (above-knee)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Foot pump + AES (above-knee) versus**	**IPCD + AES (above-knee)**	**Relative (95% CI)**	**Absolute**		
DVT (symptomatic and asymptomatic) (follow-up 5-7 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/75 (0%)	0/59 (0%)	See comment	0 fewer per 1000 (from 30 fewer to 30 more)[4]	⊕OOO VERY LOW	CRITICAL
PE (follow-up 5-7 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/75 (0%)	0/59 (0%)	See comment	0 fewer per 1000 (from 30 fewer to 30 more)[4]	⊕OOO VERY LOW	CRITICAL
Visual analogue comfort scale (range of scores: 0-10; Better indicated by lower values) (follow-up at hospital discharge – time-point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	75	59	-	MD 0.28 higher (0.69 lower to 1.25 higher)	⊕OOO VERY LOW	IMPORTANT

All-cause mortality – not reported
Major bleeding – not reported
Fatal PE – not reported

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Zero events in both arms. Risk difference calculated in Review Manager.

K.29 Cranial surgery

K.29.1 Strata: People undergoing intracranial surgery (non-tumour specific)

Table 158: Clinical evidence profile: LMWH (low dose; standard duration) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (low dose) versus UFH	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/51 (0%)	1/49 (2%)	OR 0.13 (0 to 6.55)	18 fewer per 1000 (from 20 fewer to 100 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/51 (3.9%)	0/49 (0%)	OR 7.25 (0.45 to 117.6)	Not estimable[5]	⊕OOO VERY LOW	CRITICAL
PE (follow-up 30 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/51 (0%)	0/49 (0%)	Not estimable[3]	0 fewer per 1000 (from 40 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/51 (0%)	0/49 (0%)	Not estimable[3]	0 fewer per 1000 (from 40 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/51 (3.9%)	1/49 (2%)	OR 1.9 (0.19 to 18.67)	18 more per 1000 (from 16 fewer to 260 more)	⊕OOO VERY LOW	CRITICAL
Thrombocytopenia (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/51 (3.9%)	1/49 (2%)	OR 1.9 (0.19 to 18.67)	18 more per 1000 (from 16 fewer to 260 more)	⊕OOO VERY LOW	CRITICAL

[1] 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

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

[3] Zero events in both arms

[4] Risk difference calculated in Review Manager

[5] Zero events in control arm

K.2.2 Strata: People with intracranial tumour having neurosurgery

Table 159: Clinical evidence profile: UFH versus no VTE prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UFH versus no VTE prophylaxis	Control	Relative (95% CI)	Absolute		
DVT (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/50 (6%)	17/50 (34%)	RR 0.18 (0.06 to 0.56)	279 fewer per 1000 (from 150 fewer to 320 fewer)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality – no data												
PE – no data												
Fatal PE – no data												
Major bleeding – no data												

[1] 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 160: Clinical evidence profile: LMWH (standard dose; standard duration) + IPCD versus UFH + IPCD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard) + IPCD versus UFH + IPCD	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/75 (0%)	0/75 (0%)	See comment[3]	0 fewer per 1000 (from 30 fewer to 30 more)[4]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 30 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/65 (13.8%)	5/75 (6.7%)	OR 2.21 (0.73 to 6.65)	70 more per 1000 (from 17 fewer to 255 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[5]	very serious[2]	none	2/75 (2.7%)	1/75 (1.3%)	OR 1.97 (0.2 to 19.19)	13 more per 1000 (from 11 fewer to 193 more)	⊕OOO VERY LOW	
PE – no data Fatal PE – no data												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Zero events in both arms
[4] Risk difference calculated in Review Manager
[5] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

Table 161: Clinical evidence profile: LMWH (high dose; standard duration)+IPCD versus IPCD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (high prophylactic dose)+IPCD versus IPCD**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/23 (4.3%)	1/22 (4.5%)	OR 0.96 (0.06 to 15.78)	2 fewer per 1000 (from 43 fewer to 384 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/23 (17.4%)	3/22 (13.6%)	RR 1.28 (0.32 to 5.06)	38 more per 1000 (from 93 fewer to 554 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/23 (0%)	0/22 (0%)	See comment[3]	0 fewer per 1000 (from 80 fewer to 80 more)[4]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/23 (0%)	0/22 (0%)	See comment[3]	0 fewer per 1000 (from 80 fewer to 80 more)[4]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/23 (13%)	0/22 (0%)	OR 7.77 (0.77 to 78.78)	-	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Zero events in both arms
[4] Risk difference calculated in Review Manager

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1005 **Table 162: Clinical evidence profile: LMWH (high dose; standard duration) versus IPCD**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (high dose) versus IPCD	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/21 (0%)	1/22 (4.5%)	OR 0.14 (0 to 7.15)	39 fewer per 1000 (from 45 fewer to 209 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/21 (4.8%)	3/22 (13.6%)	OR 0.36 (0.05 to 2.74)	83 fewer per 1000 (from 129 fewer to 166 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/21 (0%)	0/22 (0%)	See comment[3]	0 fewer per 1000 (from 40 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 30 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/21 (0%)	0/22 (0%)	See comment[3]	0 fewer per 1000 (from 40 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/21 (9.5%)	0/22 (0%)	OR 8.15 (0.49 to 134.79)	-	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Zero events in both arms
[4] Risk difference calculated in Review Manager

Table 163: Clinical evidence profile: IPCD versus no VTE prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up 8-10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/18 (0%)	2/5 (40%)	OR 0.01 (0 to 0.25)	393 fewer per 1000 (from 257 fewer to 400 fewer)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 8-10 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/25 (0%)	0/10 (0%)	See comment[4]	0 fewer per 1000 (from 130 fewer to 130 more)[5]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 8-10 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/25 (0%)	0/10 (0%)	See comment[4]	0 fewer per 1000 (from 130 fewer to 130 more)[5]	⊕OOO VERY LOW	CRITICAL
All-cause mortality – no data DVT – no data Major bleeding – no data												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[4] Zero events in both arms
[5] Risk difference calculated in Review Manager

K.30 Spinal injury

Table 164: Clinical evidence profile: UFH versus no VTE prophylaxis

Quality assessment							No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UFH	placebo	Relative (95% CI)	Absolute		
DVT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/16 (50%)	8/17 (47.1%)	RR 1.06 (0.53 to 2.15)	28 more per 1000 (from 221 fewer to 541 more)	VERY LOW	CRITICAL
All-cause mortality – no data reported												
Fatal PE – no data reported												
PE – no data reported												
Major bleeding – no data reported												

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

Table 165: Clinical evidence profile: LMWH (standard prophylactic dose) versus no VTE prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard dose)	no VTE prophylaxis	Relative (95% CI)	Absolute		
DVT (follow-up 12-16 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/37 (5.4%)	8/37 (21.6%)	RR 0.25 (0.06 to 1.1)	162 fewer per 1000 (from 203 fewer to 22 more)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 12-16 days)												
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[1]	none	0/37 (0%)	0/37 (0%)	Not estimable[4]	0 fewer per 1000 (from 50 fewer to 50 more)[5]	⊕OOO VERY LOW	CRITICAL

Fatal PE (follow-up 12-16 days)												
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[1]	none	0/37 (0%)	0/37 (0%)	Not estimable[4]	0 fewer per 1000 (from 50 fewer to 50 more)[5]	⊕OOO VERY LOW	CRITICAL
All-cause mortality – no data reported Major bleeding – no data reported												

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] 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
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[4] Zero events in both arms
[5] Risk difference calculated in Review Manager

Table 166: Clinical evidence profile: LMWH (standard prophylactic dose) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**UFH**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 56 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/20 (0%)	2/21 (9.5%)	Peto OR 0.14 (0.01 to 2.24)	81 fewer per 1000 (from 94 fewer to 96 more)	VERY LOW	CRITICAL
Fatal PE (follow-up 56 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/20 (0%)	2/21 (9.5%)	Peto OR 0.14 (0.01 to 2.24)	81 fewer per 1000 (from 94 fewer to 96 more)	VERY LOW	CRITICAL
DVT (follow-up 56 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/20 (0%)	3/21 (14.3%)	Peto OR 0.13 (0.01 to 1.31)	122 fewer per 1000 (from 141 fewer to 36	VERY LOW	CRITICAL

										more)		
Major bleeding (follow-up 56 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/20 (0%)	0/21 (0%)	Not estimable[4]	0 fewer per 1000 (from 90 fewer to 90 more)[5]	VERY LOW	CRITICAL
PE – no data reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[4] Zero events in both arms
[5] Risk difference calculated in Review Manager

Table 167: Clinical evidence profile: LMWH (high prophylactic dose) versus UFH+ICPD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**UFH+IPCD**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 56 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/230 (0.87%)	2/246 (0.81%)	RR 1.07 (0.15 to 7.53)	1 more per 1000 (from 7 fewer to 53 more)	VERY LOW	CRITICAL
Fatal PE (follow-up 56 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/58 (0%)	0/49 (0%)	Not estimable[3]	0 fewer per 1000 (from 40 fewer to 40 more)[4]	VERY LOW	CRITICAL
PE (follow-up 56 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/58 (5.2%)	9/49 (18.4%)	RR 0.28 (0.08 to 0.98)	132 fewer per 1000 (from 4 fewer to 169 fewer)	LOW	CRITICAL

DVT (follow-up 56 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35/58 (60.3%)	22/49 (44.9%)	RR 1.34 (0.92 to 1.95)	153 more per 1000 (from 36 fewer to 427 more)	VERY LOW	CRITICAL
Major bleeding (follow-up 56 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[5]	very serious[2]	none	6/230 (2.6%)	13/246 (5.3%)	RR 0.49 (0.19 to 1.28)	27 fewer per 1000 (from 43 fewer to 15 more)	VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Zero events in both arms.
[4] Risk difference calculated in Review Manager
[5] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

K.31 Major trauma

Table 168: Clinical evidence profile: IPCD (full leg) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPCD (full leg) versus no prophylaxis	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 7-90 days)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/215 (0.93%)	4/153 (2.6%)	RR 0.3 (0.06 to 1.62)	18 fewer per 1000 (from 25 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 7-90 days)												

2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/215 (2.3%)	15/153 (9.8%)	RR 0.26 (0.1 to 0.7)	73 fewer per 1000 (from 29 fewer to 88 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 7-90days)												
2	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/215 (0%)	1/153 (0.65%)	OR 0.07 (0 to 4.01)	6 fewer per 1000 (from 7 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 7-90 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/189 (0.53%)	1/114 (0.88%)	OR 0.59 (0.03 to 10.34)	4 fewer per 1000 (from 9 fewer to 75 more)	⊕OOO VERY LOW	CRITICAL

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

Table 169: Clinical evidence profile: IPCD (full leg) versus foot pump

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD (full leg) versus foot pump**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	6/74 (8.1%)	5/75 (6.7%)	RR 1.22 (0.39 to 3.81)	15 more per 1000 (from 41 fewer to 187 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 8 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	4/62 (6.5%)	13/62 (21%)	RR 0.31 (0.11 to 0.89)	145 fewer per 1000 (from 23 fewer to 187 fewer)	⊕OOO VERY LOW	CRITICAL

Major bleeding (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	1/74 (1.4%)	0/75 (0%)	OR 7.49 (0.15 to 377.48)	-4	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
4 Absolute effects could not be calculated due to zero events in one of the arms.

Table 170: Clinical evidence profile: IPCD (below knee) versus foot pump

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD (below knee) versus foot pump**	**Control**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up up to 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/49 (0%)	3/68 (4.4%)	OR 0.17 (0.02 to 1.76)	36 fewer per 1000 (from 43 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/49 (0%)	1/68 (1.5%)	OR 0.18 (0 to 9.51)	12 fewer per 1000 (from 15 fewer to 110 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] 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 profile: IPCD (full leg) + AES (undefined) versus no prophylaxis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPCD full leg + AES versus no prophylaxis	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up up to 3 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/32 (0%)	0/64 (0%)	See comment	0 fewer per 1000 (from 47 fewer to 47 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up up to 3 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/32 (12.5%)	2/64 (3.1%)	RR 4 (0.77 to 20.69)	94 more per 1000 (from 7 fewer to 615 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up up to 3 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/32 (0%)	1/64 (1.6%)	OR 0.22 (0 to 14.26)	12 fewer per 1000 (from 16 fewer to 169 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 172: Clinical evidence profile: Continual passive motion + UFH versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continual passive motion + UFH versus UFH	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/111 (0%)	0/116 (0%)	See comment	0 fewer per 1000 (from 17 fewer to 17 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 3 months)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/111 (3.6%)	29/116 (25%)	RR 0.14 (0.05 to 0.4)	215 fewer per 1000 (from 150 fewer to 237 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/111 (0%)	0/116 (0%)	See comment	0 fewer per 1000 (from 17 fewer to 17 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 173: Clinical evidence profile: UFH versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up up to 3 months)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/155 (0.65%)	5/205 (2.4%)	RR 0.32 (0.06 to 1.64)	17 fewer per 1000 (from 23 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up up to 3 months)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/155 (3.2%)	14/205 (6.8%)	RR 0.47 (0.17 to 1.26)	36 fewer per 1000 (from 57 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up up to 3 month)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/155 (0%)	2/205 (0.98%)	OR 0.17 (0.01 to 2.88)	8 fewer per 1000 (from 10 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL

Fatal PE (follow-up 7-90 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/92 (1.1%)	1/114 (0.88%)	OR 1.24 (0.08 to 20.32)	2 more per 1000 (from 8 fewer to 144 more)	⊕OOO VERY LOW	CRITICAL

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

Table 174: Clinical evidence profile: UFH versus IPCD (full leg)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH versus IPCD (full leg)**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up time-point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/92 (1.1%)	2/189 (1.1%)	RR 1.03 (0.09 to 11.18)	0 more per 1000 (from 10 fewer to 108 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up time-point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/92 (3.3%)	5/189 (2.6%)	RR 1.23 (0.3 to 5.05)	6 more per 1000 (from 19 fewer to 107 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up time-point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/92 (0%)	0/189 (0%)	See comment	0 fewer per 1000 (from 17 fewer to 17 more)[3]	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up time-point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/92 (1.1%)	1/189 (0.53%)	OR 2.20 (0.11 to 42.32)	6 more per 1000 (from 5 fewer to 178 more)	⊕OOO VERY	CRITICAL

											LOW	

[1] 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
[2] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Risk difference calculated in Review Manager

Table 175: Clinical evidence profile: UFH versus IPCD (full leg) + AES (undefined)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UFH versus IPCD full leg + AES	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up up to 3 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/44 (0%)	0/32 (0%)	See comment	0 fewer per 1000 (from 52 fewer to 52 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up up to 3 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/44 (2.3%)	4/32 (12.5%)	RR 0.18 (0.02 to 1.55)	102 more per 1000 (from 123 fewer to 69 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up up to 3 weeka)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/44 (0%)	0/32 (0%)	See comment	0 fewer per 1000 (from 52 fewer to 52 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

1083 **Table 176: Clinical evidence profile: LMWH (standard dose; standard dose) + IPCD (below knee) versus IPCD (below knee)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH standard dose versus IPCD	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up time-point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	8/60 (13.3%)	7/60 (11.7%)	RR 1.14 (0.44 to 2.95)	16 more per 1000 (from 65 fewer to 228 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up time-point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	3/60 (5%)	4/60 (6.7%)	RR 0.75 (0.18 to 3.21)	17 fewer per 1000 (from 55 fewer to 147 more)	⊕OOO VERY LOW	
PE (follow-up time point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/60 (0%)	0/60 (0%)	See comment	0 fewer per 1000 (from 32 fewer to 32 more)[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/60 (0%)	0/60 (0%)	See comment	0 fewer per 1000 (from 32 fewer to 32 more)[3]	⊕OOO VERY LOW	CRITICAL
								0%		-		
Fatal PE (follow-up time point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2,3]	none	4/60 (6.7%)	2/60 (3.3%)	RR 2 (0.38 to 10.51)	33 more per 1000 (from 21 fewer to 317 more)	⊕OOO VERY LOW	CRITICAL

1084 [1] 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
1085 [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
1086 [3] Risk difference calculated in Review Manager
1087 [4] Downgraded by 1 increment if the outcome does not fit the protocol

Table 177: Clinical evidence profile: LMWH (high dose; standard duration) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH versus UFH	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up mean 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/171 (1.2%)	0/173 (0%)	Peto OR 7.52 (0.47 to 120.72)	Not estimable[2]	LOW	CRITICAL
DVT (follow-up 10-14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40/129 (31%)	60/136 (44.1%)	RR 0.7 (0.51 to 0.97)	132 fewer per 1000 (from 13 fewer to 216 fewer)	MODERATE	CRITICAL
PE (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/129 (0.78%)	0/136 (0%)	Peto OR 7.8 (0.15 to 393.69)	Not estimable[2]	LOW	CRITICAL
Major bleeding (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	5/171 (2.9%)	1/173 (0.58%)	Peto OR 3.92 (0.78 to 19.63)	17 more per 1000 (from 1 fewer to 97 more)	MODERATE	CRITICAL
Fatal PE (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/171 (0%)	0/173 (0%)	Not estimable[3]	0 more per 1000 (from 113 fewer to 113 more)[4]	LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Could not be calculated as there were no events in the comparison group
[3] Could not be calculated as there were no events in the intervention or comparison group
[4] Risk difference calculated in Review Manager

Table 178: Clinical evidence profile: LMWH (high dose; standard duration) versus IPCD (below knee)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH versus IPCD	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/218 (0%)	0/224 (0%)	Not estimable[3]	0 more per 1000 (from 88 fewer to 88 more)[4]	VERY LOW	CRITICAL
DVT (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/218 (0.46%)	6/224 (2.7%)	Peto OR 0.24 (0.05 to 1.07)	20 fewer per 1000 (from 25 fewer to 2 more)	LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/218 (0.46%)	1/224 (0.45%)	Peto OR 1.03 (0.06 to 16.48)	0 more per 1000 (from 4 fewer to 64 more)	VERY LOW	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/218 (1.8%)	4/224 (1.8%)	RR 1.03 (0.26 to 4.06)	1 more per 1000 (from 13 fewer to 55 more)	VERY LOW	CRITICAL
Fatal PE – no data reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Could not be calculated as there were no events in the intervention or comparison group
[4] Risk difference calculated in Review Manager

Table 179: Clinical evidence profile: LMWH (high dose; standard duration) versus (IPCD + AES) or FID

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH versus (IPCD + AES) or FID	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/120 (0%)	0/82 (0%)	Not estimable[4]	0 per 1000 (from 202 fewer to 202 more)[5]	VERY LOW	CRITICAL
DVT (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	1/120 (0.83%)	2/82 (2.4%)	Peto OR 0.34 (0.03 to 3.40)	16 fewer per 1000 (from 24 fewer to 54 more)	VERY LOW	CRITICAL
PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/120 (0%)	0/82 (0%)	Not estimable[4]	0 per 1000 (from 202 fewer to 202 more)[5]	VERY LOW	CRITICAL
Major bleeding – no data reported Fatal PE – no data reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[4] Could not be calculated as there were no events in the intervention or comparison group
[5] Risk difference calculated in Review Manager

Table 180: Clinical evidence profile: LMWH (high dose; standard duration) versus delayed LMWH (high dose; standard duration) + foot pump

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH versus LMWH + foot pump	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/97 (0%)	0/103 (0%)	Not estimable[3]	0 per 1000 (from 194 fewer to 194 more)[5]	MODERATE	CRITICAL
DVT (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/97 (13.4%)	9/103 (8.7%)	RR 1.53 (0.69 to 3.43)	46 more per 1000 (from 27 fewer to 212 more)	VERY LOW	CRITICAL
PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/97 (2.1%)	0/103 (0%)	Peto OR 7.94 (0.49 to 128.04)	Not estimable[4]	VERY LOW	CRITICAL
Fatal PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/97 (0%)	0/103 (0%)	Not estimable[3]	0 per 1000 (from 194 fewer to 194 more)[5]	MODERATE	CRITICAL
Major bleeding – no data reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Could not be calculated as there were no events in the intervention or comparison group
[4] Could not be calculated as there were no events in the comparison group

[5] Risk difference calculated in Review Manager

K.32 Abdominal surgery (excluding bariatric surgery)

Table 181: Clinical evidence profile: AES (above knee) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES (above knee) versus no VTE prophylaxis	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up time-point not reported)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/152 (0%)	0/139 (0%)	-	0 fewer per 1000 (from 16 fewer to 16 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up time-point not reported)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/152 (7.2%)	27/139 (19.4%)	RR 0.41 (0.23 to 0.73)	115 fewer per 1000 (from 52 fewer to 150 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up time-point not reported)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/152 (0%)	1/139 (0.72%)	OR 0.13 (0 to 6.68)	6 fewer per 1000 (from 7 fewer to 39 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 182: Clinical evidence profile: AES (below knee) versus no prophylaxis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES (below knee) versus no VTE prophylaxis	Control	Relative (95% CI)	Absolute		
DVT (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/51 (3.9%)	6/44 (13.6%)	RR 0.29 (0.06 to 1.35)	97 fewer per 1000 (from 128 fewer to 48 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] 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 profile: AES (undefined) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES (undefined) versus no VTE prophylaxis	Control	Relative (95% CI)	Absolute		
DVT (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/97 (15.5%)	37/103 (35.9%)	RR 0.43 (0.25 to 0.73)	205 fewer per 1000 (from 97 fewer to 269 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] 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 184: Clinical evidence profile: AES (above knee) versus UFH

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AES (above knee) versus UFH**	**Control**	**Relative (95% CI)**	**Absolute**		
Fatal PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/52 (0%)	1/45 (2.2%)	OR 0.12 (0 to 5.9)	20 fewer per 1000 (from 22 fewer to 96 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 185: Clinical evidence profile: AES (below knee) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AES (below knee) versus UFH**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/74 (0%)	0/85 (0%)	-	0 fewer per 1000 (from 24 fewer to 24 more)[3]	⊕OOO VERY LOW	CRITICAL
PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[4]	very serious[2]	none	0/74 (0%)	0/85 (0%)	-	0 fewer per 1000 (from 24 fewer to 24 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 186: Clinical evidence profile: AES (above knee) versus AES (below knee)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES above knee versus AES below knee	Control	Relative (95% CI)	Absolute		
DVT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/56 (5.4%)	1/58 (1.7%)	RR 3.11 (0.33 to 28.99)	36 more per 1000 (from 12 fewer to 483 more)	⊕OOO VERY LOW	CRITICAL

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

Table 187: Clinical evidence profile: AES (below knee) + UFH versus AES (below knee)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES + UFH	AES	Relative (95% CI)	Absolute		
All-cause mortality (time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/89 (0%)	0/74 (0%)	-	0 fewer per 1000 (from 24 fewer to 24 more)[3]	⊕OOO VERY LOW	CRITICAL
PE (time-point not reported)												

1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/89 (0%)	0/74 (0%)	-	0 fewer per 1000 (from 24 fewer to 24 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 188: Clinical evidence profile: AES (above knee) + UFH versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES (above knee) + UFH versus UFH	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up up to 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/79 (20.3%)	11/81 (13.6%)	RR 1.49 (0.74 to 3.01)	67 more per 1000 (from 35 fewer to 273 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up up to 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/165 (1.8%)	19/171 (11.1%)	RR 0.16 (0.05 to 0.54)	93 fewer per 1000 (from 51 fewer to 106 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/175 (1.1%)	6/175 (3.4%)	RR 0.35 (0.07 to 1.68)	22 fewer per 1000 (from 32 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up mean 30 days)												
1	randomised	serious[1]	no serious	no serious	very serious[2]	none	0/86	1/90	OR 0.14 (0	10 fewer per 1000	⊕OOO	CRITICAL

	trials		inconsistency	indirectness			(0%)	(1.1%)	to 7.14)	(from 11 fewer to 63 more)	VERY LOW	

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

Table 189: Clinical evidence profile: AES (below knee) + UFH versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES (below knee) + UFH versus UFH	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/89 (0%)	0/85 (0%)	-	0 fewer per 1000 (from 22 fewer to 22 more)[3]	⊕OOO VERY LOW	CRITICAL
PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/89 (0%)	0/85 (0%)	-	0 fewer per 1000 (from 22 fewer to 22 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 190: Clinical evidence profile: AES (above knee) + IPCD versus AES (above knee)

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	AES (above knee)	Control	Relative	Absolute		

studies		bias				considerations	+ IPCD versus AES		(95% CI)			
DVT (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/38 (2.6%)	5/39 (12.8%)	RR 0.21 (0.03 to 1.68)	101 fewer per 1000 (from 124 fewer to 87 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/38 (2.6%)	1/39 (2.6%)	RR 1.03 (0.07 to 15.82)	1 more per 1000 (from 24 fewer to 380 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/38 (0%)	1/39 (2.6%)	OR 0.14 (0 to 7)	22 fewer per 1000 (from 26 fewer to 130 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] 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 profile: AES (undefined) + IPCD versus AES (undefined)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES (undefined) + IPCD versus AES	Control	Relative (95% CI)	Absolute		
DVT (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/52 (9.6%)	14/56 (25%)	RR 0.38 (0.15 to 0.99)	155 fewer per 1000 (from 2 fewer to 213 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up time-point not reported)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/52 (1.9%)	1/56 (1.8%)	RR 1.08 (0.07 to 16.78)	1 more per 1000 (from 17 fewer to 282 more)	⊕OOO VERY LOW	CRITICAL

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

Table 192: Clinical evidence profile: AES (undefined) + IPCD (full leg) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES + IPCD versus UFH	Control	Relative (95% CI)	Absolute		
DVT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/50 (6%)	7/50 (14%)	RR 0.43 (0.12 to 1.56)	80 fewer per 1000 (from 123 fewer to 78 more)	⊕OOO VERY LOW	CRITICAL

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

Table 193: Clinical evidence profile: AES (undefined) + IPCD (full leg) versus electrical stimulation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AES + IPCD versus electrical stimulation	Control	Relative (95% CI)	Absolute		

DVT											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/50 (6%)	12/50 (24%)	RR 0.25 (0.08 to 0.83)	180 fewer per 1000 (from 41 fewer to 221 fewer)	⊕⊕OO LOW	CRITICAL

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

Table 194: Clinical evidence profile: Electrical stimulation versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Electrical stimulation versus UFH**	**Control**	**Relative (95% CI)**	**Absolute**		
DVT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/50 (24%)	7/50 (14%)	RR 1.71 (0.74 to 3.99)	99 more per 1000 (from 36 fewer to 419 more)	⊕OOO VERY LOW	CRITICAL

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

Table 195: Clinical evidence profile: Foot pump versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Foot pump versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		

All-cause mortality (follow-up mean 7 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/33 (0%)	1/33 (3%)	OR 0.14 (0 to 6.82)	26 fewer per 1000 (from 30 fewer to 145 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up mean 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious	none	6/33 (18.2%)	15/33 (45.5%)	RR 0.4 (0.18 to 0.9)	273 fewer per 1000 (from 45 fewer to 373 fewer)	⊕⊕OO LOW	CRITICAL

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

Table 196: Clinical evidence profile: FID + IPCD (below knee) + LMWH (low dose) versus FID + IPCD (below knee)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FID + IPCD + LMWH versus FID + IPCD**	**Control**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up mean 11 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious$_4$	very serious[2]	none	1/16 (6.3%)	3/14 (21.4%)	RR 0.29 (0.03 to 2.5)	152 fewer per 1000 (from 208 fewer to 321 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up mean 11 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/15 (0%)	3/14 (21.4%)	OR 0.11 (0.01 to 1.13)	185 fewer per 1000 (from 212 fewer to 21 more)	⊕⊕OO LOW	CRITICAL
Thrombocytopenia (follow-up mean 6 days)												
1	randomised	serious[1]	no serious	no serious	very	none	0/16	0/14	-	0 fewer per 1000 (from	⊕OOO	IMPORTANT

	trials		inconsistency	indirectness	serious[2]		(0%)	(0%)		121 fewer to 121 more)[3]	VERY LOW	

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 197: Clinical evidence profile: IPCD (below knee) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPCD versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 42 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/55 (0%)	0/52 (0%)	-	0 fewer per 1000 (from 36 fewer to 36 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up up to 90 days)												
4	randomised trials	serious[1]	serious[4]	no serious indirectness	very serious[2]	none	27/243 (11.1%)	38/230 (16.5%)	RR 0.64 (0.26 to 1.59)	59 fewer per 1000 (from 122 fewer to 97 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up mean 42 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/181 (3.9%)	3/173 (1.7%)	RR 2.19 (0.58 to 8.24)	21 more per 1000 (from 7 fewer to 126 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up up to 90 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/159 (0.63%)	2/154 (1.3%)	OR 0.5 (0.05 to 4.81)	6 fewer per 1000 (from 12 fewer to 47 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager
[4] Unexplained heterogeneity

Table 198: Clinical evidence profile: IPCD (full leg) versus IPCD (below knee)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPCD full length versus IPCD below knee	Control	Relative (95% CI)	Absolute		
DVT (follow-up mean 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/47 (0%)	1/43 (2.3%)	OR 0.12 (0 to 6.24)	20 fewer per 1000 (from 23 fewer to 106 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up mean 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/47 (2.1%)	0/43 (0%)	OR 6.79 (0.13 to 343.33)	-	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up mean 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/47 (0%)	1/43 (2.3%)	OR 0.12 (0 to 6.24)	20 fewer per 1000 (from 23 fewer to 106 more)	⊕OOO VERY LOW	CRITICAL

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

Table 199: Clinical evidence profile: IPCD (full leg) versus VKA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPCD versus warfarin	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 7-14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/47 (0%)	0/53 (0%)	-	0 fewer per 1000 (from 38 fewer to 38 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 7-14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/47 (4.3%)	0/53 (0%)	OR 8.58 (0.53 to 139.81)	-	⊕OOO VERY LOW	CRITICAL
PE (follow-up 7-14 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	1/47 (2.1%)	0/53 (0%)	OR 8.4 (0.17 to 426.1)	-	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 200: Clinical evidence profile: IPCD (undefined) + LMWH (standard dose) versus IPCD (undefined)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPCD + LMWH standard dose	Control	Relative (95% CI)	Absolute		

							versus IPCD					
DVT (follow-up 12-30 days)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/191 (0.52%)	9/143 (6.3%)	RR 0.07 (0.02 to 0.26)	59 fewer per 1000 (from 47 fewer to 62 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 12-30 days)												
2	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/191 (0%)	0/143 (0%)	-	0 fewer per 1000 (from 12 fewer to 12 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 201: Clinical evidence profile: UFH versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 5-8 days)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/197 (1.5%)	9/196 (4.6%)	RR 0.36 (0.1 to 1.27)	29 fewer per 1000 (from 41 fewer to 12 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 7-70 days)												
12	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/983 (5.5%)	139/1008 (13.8%)	RR 0.4 (0.30 to 0.53)	83 fewer per 1000 (from 65 fewer to 97 fewer)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up 7-70 days)												

10	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/447 (3.8%)	28/450 (6.2%)	RR 0.60 (0.36 to 1.02)	25 fewer per 1000 (from 40 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 6-14 days)												
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31/419 (7.4%)	23/306 (7.5%)	RR 1.30 (0.84 to 2)	23 more per 1000 (from 12 fewer to 75 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 7-70 days)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/247 (0%)	1/259 (0.39%)	OR 0.15 (0 to 7.52)	3 fewer per 1000 (from 4 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL

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

Table 202: Clinical evidence profile: UFH versus IPCD (below knee)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH versus IPCD**	**Control**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up mean 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/135 (8.9%)	5/130 (3.8%)	RR 2.36 (0.87 to 6.44)	52 more per 1000 (from 5 fewer to 209 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up mean 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/135 (0.74%)	1/130 (0.77%)	OR 1.04 (0.06 to 17)	0 more per 1000 (from 7 fewer to 109 more)	⊕OOO VERY LOW	CRITICAL

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

Table 203: Clinical evidence profile: UFH versus VKA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UFH versus VKA	Control	Relative (95% CI)	Absolute		
DVT (follow-up mean 7 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/99 (4%)	12/98 (12.2%)	RR 0.33 (0.11 to 1)	82 fewer per 1000 (from 109 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/50 (0%)	0/50 (0%)	-	0 fewer per 1000 (from 38 fewer to 38 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 204: Clinical evidence profile: LMWH (low dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH low dose versus no prophlyaxis	Control	Relative (95% CI)	Absolute		

All-cause mortality (follow-up mean 42 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/95 (0%)	2/88 (2.3%)	OR 0.12 (0.01 to 1.99)	20 fewer per 1000 (from 22 fewer to 22 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up mean 42 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/95 (4.2%)	14/88 (15.9%)	RR 0.26 (0.09 to 0.77)	118 fewer per 1000 (from 37 fewer to 145 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up mean 42 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/95 (0%)	2/88 (2.3%)	OR 0.12 (0.01 to 1.99)	20 fewer per 1000 (from 22 fewer to 22 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up mean 42 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/95 (4.2%)	4/88 (4.5%)	RR 0.93 (0.24 to 3.59)	3 fewer per 1000 (from 35 fewer to 118 more)	⊕OOO VERY LOW	CRITICAL
Thrombocytopenia (follow-up mean 42 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/95 (0%)	0/88 (0%)	-	0 fewer per 1000 (from 21 fewer to 21 more)[3]	⊕OOO VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 205: Clinical evidence profile: LMWH (low dose; standard duration) versus UFH

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH low dose versus UFH	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 6-56 days)												
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	86/3509 (2.5%)	68/3514 (1.9%)	RR 1.27 (0.93 to 1.74)	5 more per 1000 (from 1 fewer to 14 more)	⊕⊕OO LOW	CRITICAL
DVT (follow-up 6-30 days)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54/1530 (3.5%)	28/1515 (1.8%)	RR 1.91 (1.22 to 3.00)	17 more per 1000 (from 4 more to 37 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 6-30 days)												
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/3420 (0.38%)	15/3416 (0.44%)	OR 0.87 (0.41 to 1.83)	1 fewer per 1000 (from 3 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 5-30 days)												
7	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	127/3344 (3.8%)	174/3350 (5.2%)	RR 0.73 (0.49 to 1.11)	14 fewer per 1000 (from 26 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 6-30 days)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/2919 (0.24%)	4/2929 (0.14%)	OR 1.75 (0.54 to 5.71)	1 more per 1000 (from 1 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Unexplained heterogeneity

Table 206: Clinical evidence profile: LMWH (standard dose; standard duration) versus no prophylaxis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH standard dose versus no prophylaxis	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up mean 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/39 (0%)	2/41 (4.9%)	OR 0.14 (0.01 to 2.26)	42 fewer per 1000 (from 48 fewer to 55 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 7-30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/64 (4.7%)	9/66 (13.6%)	RR 0.35 (0.1 to 1.2)	89 fewer per 1000 (from 123 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 14-30 days)												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	0/64 (0%)	1/66 (1.5%)	OR 0.14 (0 to 7.17)	13 fewer per 1000 (from 15 fewer to 84 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 14-30 days)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/297 (3.7%)	2/230 (0.87%)	OR 2.90 (0.90 to 9.34)	16 more per 1000 (from 1 fewer to 67 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 207: Clinical evidence profile: LMWH (standard dose; standard duration) versus IPCD (undefined)

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	LMWH low dose	Control	Relative	Absolute		

studies		bias				considerations	versus IPCD		(95% CI)			
DVT (follow-up mean 5 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/105 (1.9%)	1/106 (0.94%)	OR 1.98 (0.2 to 19.23)	9 more per 1000 (from 8 fewer to 145 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up mean 5 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/105 (0%)	0/106 (0%)	-	0 fewer per 1000 (from 18 fewer to 18 more)[3]	⊕OOO VERY LOW	CRITICAL
Thrombocytopenia (follow-up mean 3 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/105 (1.9%)	4/106 (3.8%)	RR 0.5 (0.09 to 2.7)	19 fewer per 1000 (from 34 fewer to 64 more)	⊕OOO VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 208: Clinical evidence profile: LMWH (standard dose; standard duration) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH standard dose versus UFH	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 8-30 days)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	25/1259 (2%)	24/1252 (1.9%)	RR 1.04 (0.60 to 1.80)	1 more per 1000 (from 8 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 7-56 days)												

8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/1429 (3.4%)	57/1427 (4%)	RR 0.85 (0.59 to 1.24)	6 fewer per 1000 (from 16 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 7-56 days)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/1682 (0.12%)	11/1678 (0.66%)	OR 0.24 (0.08 to 0.73)	5 fewer per 1000 (from 2 fewer to 6 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding (follow-up 8-30 days)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	74/1577 (4.7%)	44/1573 (2.8%)	RR 1.69 (1.19 to 2.41)	19 more per 1000 (from 5 more to 39 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/505 (0%)	1/497 (0.2%)	OR 0.13 (0.00 to 6.71)	2 fewer per 1000 (from 2 fewer to 11 more)	⊕OOO VERY LOW	CRITICAL

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

Table 209: Clinical evidence profile: LMWH (high dose; standard duration) versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH high dose**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	031 (0%)	-	0 fewer per 1000 (from 62 fewer to 62 more)	⊕OOO VERY	CRITICAL

											LOW	
DVT (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/30 (6.7%)	11/31 (35.5%)	RR 0.19 (0.05 to 0.78)	287 fewer per 1000 (from 78 fewer to 337 fewer)	⊕⊕OO LOW	CRITICAL

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

Table 210: Clinical evidence profile: LMWH (high dose; standard duration) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH high dose versus UFH**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/23 (0%)	0/20 (0%)	-	0 fewer per 1000 (from 87 fewer to 87 more)[3]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/23 (0%)	0/20 (0%)	-	0 fewer per 1000 (from 87 fewer to 87 more)[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/23 (26.1%)	1/20 (5%)	RR 5.22 (0.68 to 39.74)	211 more per 1000 (from 16 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

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1262 **Table 211: Clinical evidence profile: LMWH (low dose; standard duration) versus LMWH (standard dose; standard duration)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH low dose versus LMWH standard dose	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 8-30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	45/1465 (3.1%)	42/1466 (2.9%)	RR 1.07 (0.7 to 1.62)	2 more per 1000 (from 9 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 7-30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	142/1423 (10%)	72/1430 (5%)	RR 1.98 (1.51 to 2.59)	49 more per 1000 (from 26 more to 80 more)	⊕⊕⊕O MODERATE	CRITICAL
PE (follow-up mean 30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/1423 (0.56%)	7/1430 (0.49%)	OR 1.15 (0.42 to 3.16)	1 more per 1000 (from 3 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up mean 30 days)												
3	randomised trials	serious[1]	serious[3]	serious[4]	very serious[2]	none	17/1481 (1.1%)	24/1485 (1.6%)	RR 0.58 (0.14 to 2.41)	7 fewer per 1000 (from 14 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up mean 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/16 (0%)	0/19 (0%)	-	0 fewer per 1000 (from 106 fewer to 106 more)[5]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Unexplained heterogeneity
[4] Indirect as outcome with most weight includes 'blood loss'
[5] Risk difference calculated in Review Manager

Table 212: Clinical evidence profile: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extended duration LMWH standard dose versus standard duration LMWH standard dose	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 60 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/165 (1.8%)	6/167 (3.6%)	RR 0.51 (0.13 to 1.99)	18 fewer per 1000 (from 31 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 25-31 days days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/165 (4.8%)	20/167 (12%)	RR 0.43 (0.18 to 0.89)	68 fewer per 1000 (from 13 fewer to 98 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/165 (0%)	2/167 (1.2%)	OR 0.14 (0.01 to 2.19)	10 fewer per 1000 (from 12 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up up to 90 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/458 (0.87%)	5/470 (1.1%)	OR 0.83 (0.22 to 3.08)	2 fewer per 1000 (from 8 fewer to 21 more)	⊕OOO VERY LOW	CRITICAL

Fatal PE (follow-up 90 days)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/165 (0%)	1/167 (0.6%)	OR 0.14 (0.00 to 6.90)	5 fewer per 1000 (from 6 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL

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

Table 213: Clinical evidence profile: LMWH (high dose; extended duration) versus LMWH (high dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Extended duration LMWH high dose versus standard duration LMWH high dose**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 90 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/248 (3.2%)	6/240 (2.5%)	RR 1.29 (0.45 to 3.66)	7 more per 1000 (from 14 fewer to 67 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up mean 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/248 (7.7%)	29/240 (12.1%)	RR 0.63 (0.37 to 1.10)	45 fewer per 1000 (from 76 fewer to 12 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up mean 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/248 (0%)	0/240 (0%)	-	0 fewer per 1000 (from 8 fewer to 8 more)[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up mean 22 days)												
1	randomised	no serious	no serious	no serious	very	none	2/315	1/310	OR 1.92	3 more per 1000	⊕⊕OO	CRITICAL

	trials	risk of bias	inconsistency	indirectness	serious[2]		(0.63%)	(0.32%)	(0.20 to 18.54)	(from 3 fewer to 53 more)	LOW	

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 214: Clinical evidence profile: LMWH (standard dose; extended duration) + AES (undefined) versus LMWH (standard dose; standard duration) + AES (undefined)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH standard dose extended duration + AES	LMWH standard dose standard duration + AES	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 60 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/205 (9.8%)	17/222 (7.7%)	RR 1.27 (0.69 to 2.36)	21 more per 1000 (from 24 fewer to 104 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 60 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/165 (7.3%)	26/175 (14.9%)	RR 0.49 (0.26 to 0.94)	76 fewer per 1000 (from 9 fewer to 110 fewer)	⊕⊕OO LOW	CRITICAL
PE (follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/165 (0%)	3/178 (1.7%)	RR 0.14 (0.01 to 1.40)	14 fewer per 1000 (from 17 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/205 (0%)	0/222 (0%)	-	0 fewer per 1000 (from 9 fewer to 9 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference calculated in Review Manager

Table 215: Clinical evidence profile: Fondaparinux versus LMWH (standard dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fondaparinux versus LMWH standard dose	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up mean 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40/1433 (2.79%)	55/1425 (3.9%)	RR 0.72 (0.48 to 1.08)	11 fewer per 1000 (from 20 fewer to 3 more)	⊕⊕OO LOW	CRITICAL
DVT (follow-up mean 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43/1024 (4.2%)	59/1018 (5.8%)	RR 0.72 (0.49 to 1.06)	16 fewer per 1000 (from 30 fewer to 3 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up mean 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/1465 (0.14%)	0/1462 (0%)	OR 7.38 (0.46 to 118.03)	-	⊕OOO VERY LOW	CRITICAL

Major bleeding (follow-up mean 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/1433 (3.4%)	34/1425 (2.4%)	RR 1.43 (0.93 to 2.21)	10 more per 1000 (from 2 fewer to 29 more)	⊕⊕OO LOW	CRITICAL
Fatal PE (follow-up mean 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/1465 (0.2%)	3/1462 (0.21%)	OR 1 (0.2 to 4.95)	0 fewer per 1000 (from 2 fewer to 8 more)	⊕OOO VERY LOW	CRITICAL

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

Table 216: Clinical evidence profile: Fondaparinux + IPCD (undefined) versus IPCD (undefined)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fondaparinux + IPCD versus IPCD**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 32 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/635 (1.3%)	5/650 (0.77%)	OR 1.63 (0.55 to 4.86)	5 more per 1000 (from 3 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up mean 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/424 (1.7%)	22/418 (5.3%)	RR 0.31 (0.14 to 0.73)	36 fewer per 1000 (from 14 fewer to 45 fewer)	⊕⊕⊕O MODERATE	CRITICAL

PE (follow-up mean 32 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/424 (0.31%)	3/418 (0.62%)	OR 0.36 (0.05 to 2.57)	5 fewer per 1000 (from 7 fewer to 11 more)	⊕OOO VERY LOW	CRITICAL
Fatal PE (follow-up mean 32 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/635 (0.16%)	1/650 (0.15%)	OR 1.02 (0.06 to 16.39)	0 more per 1000 (from 1 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL

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

Table 217: Fondaparinux versus no prophylaxis/mechanical

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fondaparinux + IPCD versus IPCD**	**Control**	**Relative (95% CI)**	**Absolute**		
Major bleeding (follow-up mean 32 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/635 (1.6%)	1/650 (0.15%)	OR 5.33 (1.63 to 17.45)	7 more per 1000 (from 1 more to 25 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] 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 218: Fondaparinux + UFH + mechanical (AES + IPCD) versus LMWH + UFH + mechanical (AES + IPCD)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fonda + UFH + mech**	**LMWH + UFH + mech**	**Relative (95% CI)**	**Absolute**		
PE (follow-up not reported)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/130 (0%)	2/128 (1.6%)	OR 0.13 (0.01 to 2.13)	14 fewer per 1000 (from 15 fewer to 17 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up not reported)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/152 (1.3%)	1/146 (0.68%)	OR 1.88 (0.19 to 18.21)	6 more per 1000 (from 6 fewer to 105 more)	⊕OOO VERY LOW	CRITICAL

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

Table 219: VKA versus no prophylaxis

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VKA versus no prophylaxis**	**Control**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/48 (6.3%)	11/48 (22.9%)	RR 0.27 (0.08 to 0.92)	167 fewer per 1000 (from 18 fewer to 211 fewer)	⊕⊕OO LOW	CRITICAL

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

K.33 Bariatric surgery

Table 220: Clinical evidence profile: LMWH (standard pre-op, high post-op) versus fondaparinux

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (standard pre-op, high post-op)	fondaparinux	Relative (95% CI)	Absolute		
DVT (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/83 (2.4%)	2/94 (2.1%)	RR 1.13 (0.16 to 7.86)	3 more per 1000 (from 18 fewer to 146 more)	⊕OOO VERY LOW	CRITICAL
Thrombocytopenia (follow-up 14 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/83 (0%)	1/94 (1.1%)	OR 0.15 (0 to 7.73)	9 fewer per 1000 (from 11 fewer to 66 more)	⊕OOO VERY LOW	IMPORTANT
All-cause mortality – not reported PE – not reported Fatal PE – not reported Major bleeding – not reported												

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

Table 221: Clinical evidence profile: LMWH (very high dose; standard duration) versus LMWH (high dose; standard duration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (very high dose)	LMWH (high dose)	Relative (95% CI)	Absolute		
DVT (symptomatic and asymptomatic) (follow-up 90 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/30 (0%)	0/30 (0%)	See comment[3]	0 fewer per 1000 (from 60 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up time-point unclear)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	2/30 (6.7%)	0/30 (0%)	OR 7.65 (0.47 to 125.22)	-[5]	⊕OOO VERY LOW	CRITICAL
All-cause mortality – not reported PE – not reported Fatal PE – not reported												

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Zero events in both arms. Risk difference calculated in Review Manager.
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[5] Absolute effects could not be calculated due to zero events in one of the arms

Table 222: Clinical evidence profile: LMWH (very high dose; standard duration) + IPCD + AES versus LMWH (high dose; standard duration) + IPCD + AES

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH (very high dose) + IPCD + AES	LMWH (high dose) + IPCD + AES	Relative (95% CI)	Absolute		

All-cause mortality (follow-up 90 days)											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	0/119 (0%)	0/131 (0%)	See comment[2]	0 fewer per 1000 (from 20 fewer to 20 more)[2]	⊕OOO VERY LOW	CRITICAL
DVT (symptomatic and asymptomatic) (follow-up 11 days)											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	1/119 (0.84%)	1/131 (0.76%)	OR 1.1 (0.07 to 17.76)	1 more per 1000 (from 7 fewer to 113 more)	⊕OOO VERY LOW	CRITICAL
PE (follow-up 11 days)											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	0/119 (0%)	1/131 (0.76%)	OR 0.15 (0 to 7.51)	6 fewer per 1000 (from 8 fewer to 47 more)	⊕OOO VERY LOW	CRITICAL
Heparin-induced thrombocytopenia (follow-up 11 days)											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	1/119 (0.84%)	1/131 (0.76%)	OR 1.1 (0.07 to 17.76)	1 more per 1000 (from 7 fewer to 113 more)	⊕OOO VERY LOW	IMPORTANT
	Major bleeding – not reported Fatal PE – not reported											

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Zero events in both arms. Risk difference calculated in Review Manager
[3] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

K.34 Cardiac surgery

Table 223: Clinical evidence profile: IPCD + AES + aspirin vs AES + aspirin for VTE prophylaxis in people undergoing cardiac surgery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPCD + AES + aspirin	AES + aspirin	Relative (95% CI)	Absolute		
All-cause mortality (follow-up until discharge)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	2/164 (1.2%)	0/166 (0%)	OR 7.53 (0.47 to 120.83)	-[3]	VERY LOW	CRITICAL
DVT (follow-up ≥4 days post-op until discharge)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	31/164 (18.9%)	36/166 (21.7%)	RR 0.87 (0.57 to 1.34)	28 fewer per 1000 (from 93 fewer to 74 more)	VERY LOW	CRITICAL
PE (follow-up until discharge)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/164 (0.61%)	1/166 (0.6%)	RR 1.01 (0.06 to 16.05)	0 more per 1000 (from 6 fewer to 91 more)	VERY LOW	CRITICAL
PE, fatal (follow-up until discharge)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/164 (0.61%)	1/165 (0.61%)	OR 1.01 (0.06 to 16.15)	0 more per 1000 (from 6 fewer to 84 more)	VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Zero events in control arm

Table 224: Clinical evidence profile: Aspirin versus no prohylaxis for VTE prophylaxis in people undergoing cardiac surgery

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin versus no	Control	Relative	Absolute		

studies						considerations	prophylaxis		(95% CI)			
All-cause mortality (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	14/1047 (1.3%)	9/1053 (0.85%)	RR 1.56 (0.68 to 3.6)	5 more per 1000 (from 3 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/1047 (0.76%)	10/1053 (0.95%)	RR 0.8 (0.32 to 2.03)	2 fewer per 1000 (from 6 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	19/1047 (1.8%)	22/1053 (2.1%)	RR 0.87 (0.47 to 1.6)	3 fewer per 1000 (from 11 fewer to 13 more)	⊕⊕OO LOW	CRITICAL

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

Table 225: Clinical evidence profile: Fondaparinux + AES and/or IPCD versus AES and/or IPCD alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fonda + AES/IPCD versus AES/IPCD	Control	Relative (95% CI)	Absolute		
DVT (follow-up 9-11 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/35 (0%)	1/32 (3.1%)	OR 0.12 (0 to 6.23)	27 fewer per 1000 (from 31 fewer to 136 more)	⊕⊕OO LOW	CRITICAL

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

K.35 Thoracic surgery

No relevant clinical studies were identified.

K.36 Vascular surgery

K.36.1 Unstratified data

Table 226: Clinical evidence profile: UFH versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UFH	No prophylaxis	Relative (95% CI)	Absolute		
DVT (follow-up not reported)												
2	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	6/48 (12.5%)	10/44 (22.7%)	RR 0.57 (0.22 to 1.46)	98 fewer per 1000 (from 177 fewer to 105 more)	⊕OOO VERY LOW	CRITICAL
Pulmonary embolism (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	1/24 (4.2%)	0/19 (0%)	not pooled	not pooled	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up not reported)												
2	randomised trials	serious[1]	no serious inconsistency	very serious[3]	serious[3]	none	8/48 (16.7%)	1/44 (2.3%)	RR 8.33 (1.13 to 61.7)	167 more per 1000 (from 3 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 227: Clinical evidence profile: LMWH versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH	UFH	Relative (95% CI)	Absolute		
All-cause mortality (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/122 (1.6%)	0/111 (0%)	RR 4.55 (0.22 to 93.81)	-	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	10/122 (8.2%)	4/111 (3.6%)	RR 2.27 (0.73 to 7.05)	46 more per 1000 (from 10 fewer to 218 more)	⊕OOO VERY LOW	CRITICAL
Pulmonary embolism (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/122 (0%)	0/111 (0%)	See comment	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Thrombocytopenia (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/122 (1.6%)	0/111 (0%)	OR 6.81 (0.42 to 109.84)	-	⊕OOO VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Zero events in both arms. Risk difference calculated in Review Manager

Strata: Varicose vein surgery

Table 228: Clinical evidence profile: LMWH +AES+IPCD+ mobilisation versus IPCD/AES+mobilisation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH +AES +IPCD +mobilisation	IPCD/AES +mobilisation	Relative (95% CI)	Absolute		
DVT (follow-up 90 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/130 (0%)	0/132 (0%)	See comment[3]	0 fewer per 1000 (from 10 fewer to 10 more)[3]	⊕OOO VERY LOW	CRITICAL
PE (follow-up 90 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/130 (0%)	0/132 (0%)	See comment[3]	0 fewer per 1000 (from 10 fewer to 10 more)[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up 90 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/130 (0%)	0/132 (0%)	See comment[3]	0 fewer per 1000 (from 10 fewer to 10 more)[3]	⊕OOO VERY LOW	CRITICAL

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

Table 229: Clinical evidence profile: LMWH (high dose) versus no prophylaxis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (high dose)**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/550 (0.36%)	28/542 (5.2%)	RR 0.07 (0.02 to 0.29)	48 fewer per 1000 (from 37 fewer to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/550 (0%)	8/542 (1.5%)	OR 0.13 (0.03 to 0.53)	13 fewer per 1000 (from 7 fewer to 14 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/550 (0.18%)	1/542 (0.18%)	OR 0.99 (0.06 to 15.78)	0 fewer per 1000 (from 2 fewer to 26 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 230: Clinical evidence profile: UFH versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UFH**	**No prophylaxis**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/531 (0.56%)	28/542 (5.2%)	RR 0.11 (0.03 to 0.36)	46 fewer per 1000 (from 33 fewer to 50 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/531 (0%)	8/542 (1.5%)	OR 0.14 (0.03 to 0.55)	13 fewer per 1000 (from 7 fewer to 14 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/531 (0%)	1/542 (0.18%)	OR 0.14 (0 to 6.96)	2 fewer per 1000 (from 2 fewer to 11 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 231: Clinical evidence profile: LMWH (high dose) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (high dose)**	**UFH**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/550 (0.36%)	3/531 (0.56%)	RR 0.64 (0.11 to 3.84)	2 fewer per 1000 (from 5 fewer to 16 more)	⊕⊕OO LOW	CRITICAL
PE (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/550 (0%)	0/531 (0%)	See comment[2]	-[2]	⊕⊕OO LOW	CRITICAL
Major bleeding (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[1]	none	1/550 (0.18%)	4/531 (0.75%)	OR 0.29 (0.05 to 1.68)	5 fewer per 1000 (from 7 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Zero events in both arms. Risk difference calculated in Review Manager
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

Table 232: Clinical evidence profile: AES versus no prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varicose vein strata - AES	No prophylaxis	Relative (95% CI)	Absolute		
Mortality (follow-up 2 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/200 (0%)	0%	-	0 fewer per 1000 (from 10 fewer to 10 more)[2]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 2 weeks; assessed with: ultrasound duplex)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/200 (0%)	0%	-	0 fewer per 1000 (from 10 fewer to 10 more)[2]	⊕OOO VERY LOW	CRITICAL
Symptomatic pulmonary embolism (follow-up 2 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/200 (0%)	0%	-	0 fewer per 1000 (from 10 fewer to 10 more)[2]	⊕OOO VERY LOW	CRITICAL
HRQOL (AVVSS) (follow-up 4 weeks; measured with: Aberdeen Varicose Vein Symptoms Severity Score; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	200	200	-	MD 0.5 higher (0.19 lower to 1.19 higher)	⊕⊕⊕O MODERATE	IMPORTANT
HRQOL (VCSS) (follow-up 7 days; measured with: Venous clinical severity score; range of scores: 0-30; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4]	none	39	46	-	MD 1.23 lower (4.72 lower to 2.26 higher)	⊕OOO VERY LOW	IMPORTANT
HRQOL (CIVIQ-2) (follow-up 90 days; measured with: Chronic venous insufficiency questionnaire; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4]	none	39	46	-	MD 6.6 higher (7.67 lower to 20.87 higher)	⊕OOO VERY LOW	IMPORTANT

[1] 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
[2] Zero events in both arms. Risk difference calculated in Review Manager
[3] Some people were included in the study twice if they required bilateral treatment (number of people = 70, number of cases = 85)
[4] Unable to calculate as standard deviations not reported

Strata: Lower limb amputation

Table 233: Clinical evidence profile: LMWH (standard dose) versus UFH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH (standard dose)**	**UFH**	**Relative (95% CI)**	**Absolute**		
DVT (follow-up 5-8 days post-op)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/41 (9.8%)	4/34 (11.8%)	RR 0.83 (0.22 to 3.07)	20 fewer per 1000 (from 92 fewer to 244 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[3]	very serious[2]	none	0/41 (0%)	0/34 (0%)	See comment[4]	0 fewer per 1000 (from 50 fewer to 50 more)[4]	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes
[4] Zero events in both arms. Risk difference calculated in Review Manager

K.37 Head and neck surgery

K.37.1 Oral and maxillofacial surgery

No relevant clinical studies were identified.

K.37.2 Ear, nose and throat (ENT) surgery

No relevant clinical studies were identified.

Appendix L:Forest plots

L.1 Risk assessment for people admitted to hospital

L.1.1 Patients admitted to hospital

L.1.1.1 VTE

L.1.1.1.1 General medical patients

Caprini risk assessment model

Table 234: Sensitivity and specificity plot for the Caprini risk assessment model at a cut-off of 5 in general medical patients for VTE

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Grant 2016	467	30903	203	31251	0.70 [0.66, 0.73]	0.50 [0.50, 0.51]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Table 235: Sensitivity and specificity plot for the Caprini risk assessment model at a cut-off of 7 in general medical patients for VTE

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Grant 2016	286	15902	384	46977	0.43 [0.39, 0.47]	0.75 [0.74, 0.75]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Table 236: Sensitivity and specificity plot for the Caprini risk assessment model at a cut-off of 9 in general medical patients for VTE

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Grant 2016	124	6896	546	55966	0.19 [0.16, 0.22]	0.89 [0.89, 0.89]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Geneva Risk Score

Figure 1: Sensitivity and specificity plot for the Geneva Risk Score in general medical patients for VTE

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Nendaz 2014	31	934	3	510	0.91 [0.76, 0.98]	0.35 [0.33, 0.38]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

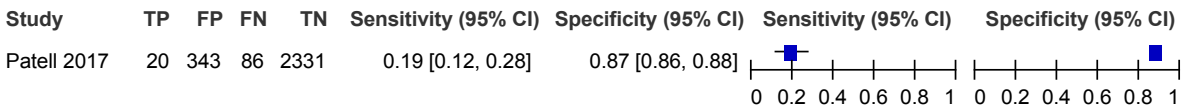
Padua Prediction Score

Figure 2: Sensitivity and specificity plot for the Padua Prediction Score in general medical patients for VTE

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Nendaz 2014	25	695	9	749	0.74 [0.56, 0.87]	0.52 [0.49, 0.54]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Khorana Score for hospitalised cancer patients

Figure 3: Sensitivity and specificity plot for the Khorana Score in oncology inpatients for VTE with a cut-off of ≥3

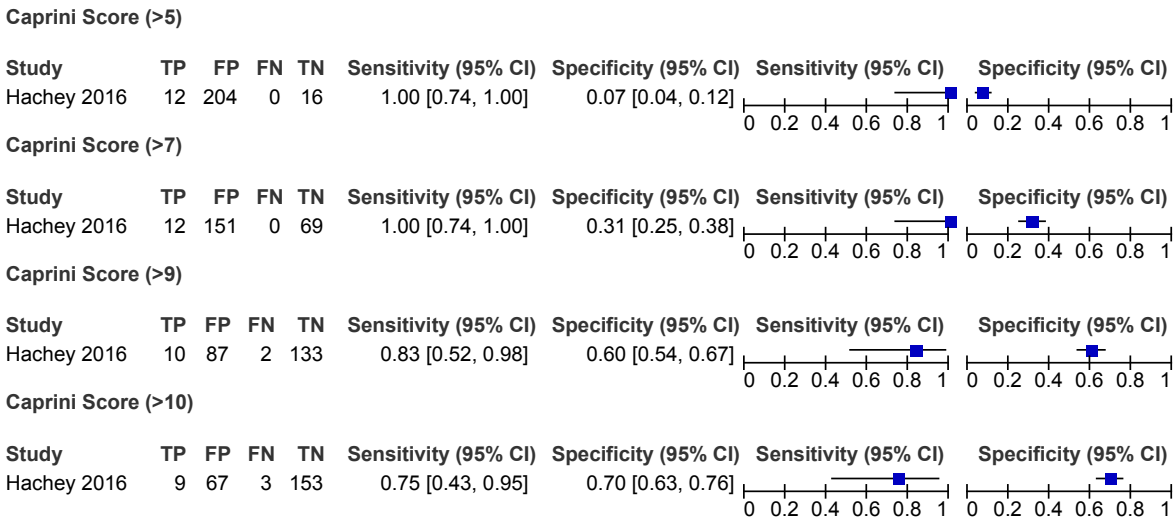


L.1.1.2 Surgical patients

L.1.1.2.1 People undergoing lung cancer resection

Caprini risk assessment model

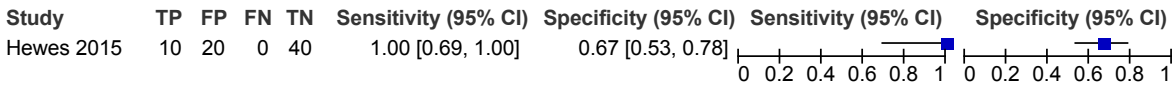
Figure 4: Sensitivity and specificity plot for the Caprini Score in lung cancer surgery patients for VTE



L.1.1.2.2 Oesophageal cancer surgery patients

Modified Caprini risk assessment model

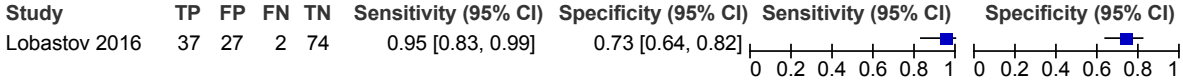
Figure 5: Sensitivity and specificity plot for the Modified Caprini Score with a cut off of 15 in oesophageal cancer surgery patients for VTE



L.1.1.2.3 High-risk patients undergoing emergency abdominal surgery or neurosurgery

Caprini risk assessment model

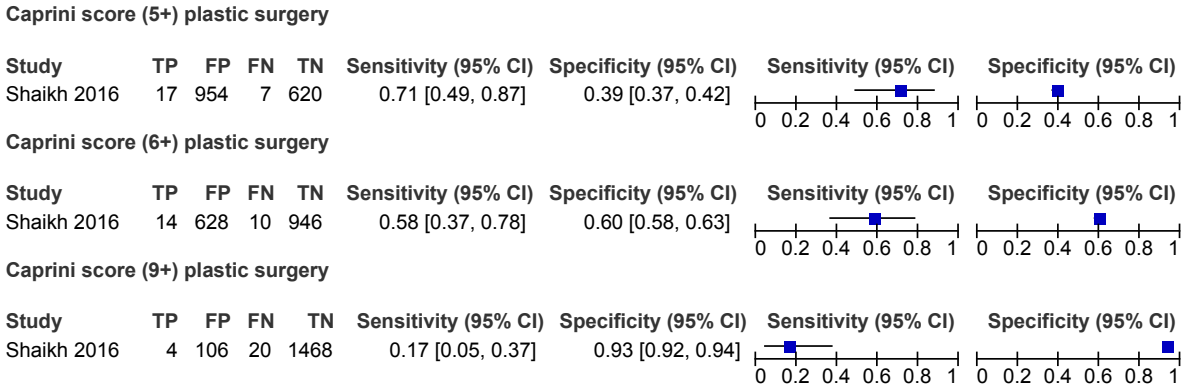
Figure 6: Sensitivity and specificity plot for the Caprini Score with a cut off of 10.5 in high-risk patients undergoing emergency abdominal or neurosurgery



L.1.1.2.4 People undergoing plastic surgery

Caprini risk assessment model

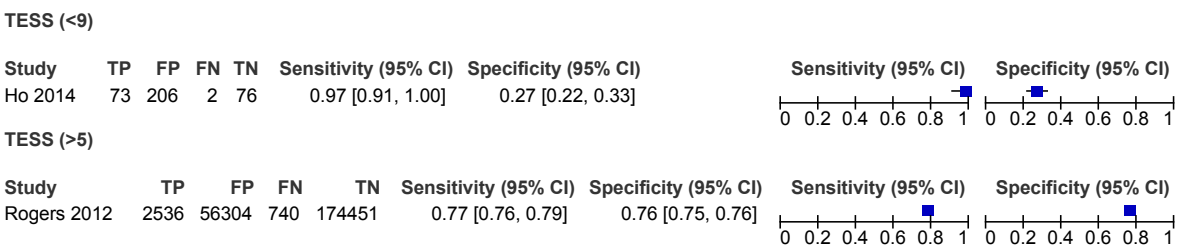
Figure 7: Sensitivity and specificity plot for the Caprini score for people undergoing plastic surgery



L.1.1.3 People with trauma

L.1.1.3.1 Trauma Embolic Severity Score (TESS)

Figure 8: Sensitivity and specificity plot for TESS in people with trauma for VTE

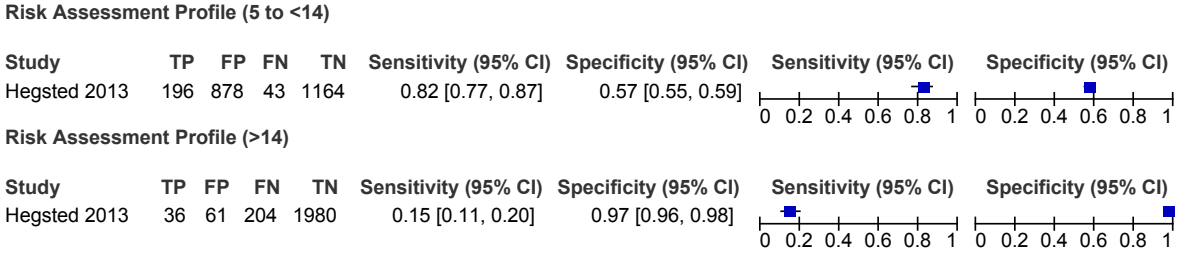


L.1.1.4 DVT

L.1.1.4.1 People with trauma

Risk Assessment Profile

Figure 9: Sensitivity and specificity plot for the Risk Assessment Profile in people with trauma for DVT

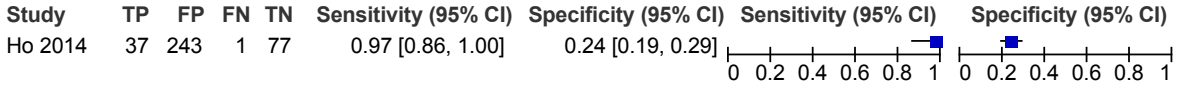


L.1.1.5 PE (fatal and non-fatal PE)

L.1.1.5.1 People with trauma

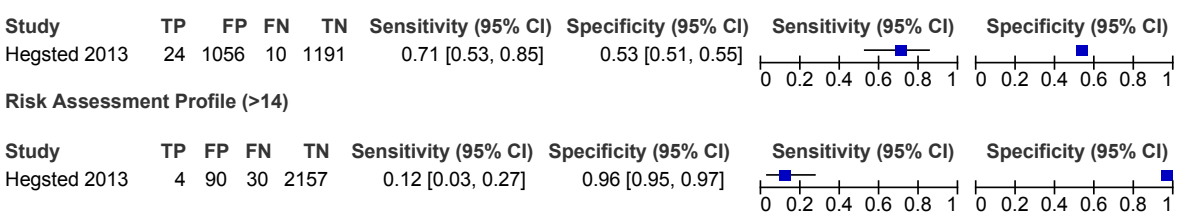
Trauma Embolic Severity Score (TESS)

Figure 10: Sensitivity and specificity plot for TESS with a cut-off of 9 in people with trauma for PE (fatal and non-fatal PE)



Risk Assessment Profile

Figure 11: Sensitivity and specificity plot for the Risk Assessment Profile n people with trauma for PE (fatal and non-fatal PE)

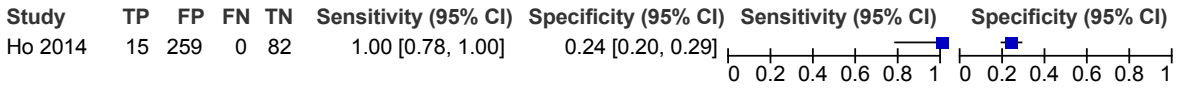


L.1.1.6 Fatal PE

L.1.1.6.1 People with trauma

TESS

Figure 12: Sensitivity and specificity plot for TESS with a cut-off of 9 in people with trauma for fatal PE



L.1.2 Hospital admissions

L.1.2.1 Coupled sensitivity and specificity forest plots

Figure 13: Sensitivity and specificity of the IMPROVE bleeding risk tool for predicting major bleeding at 14 days

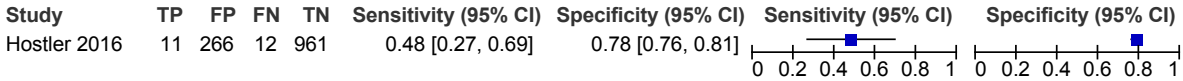
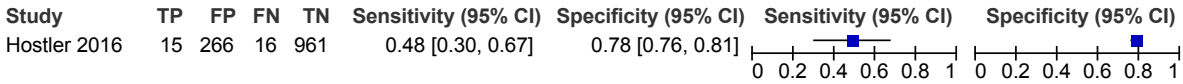


Figure 14: Sensitivity and specificity of the IMPROVE bleeding risk tool for predicting major bleeding during hospitalisation



L.1.3 Risk assessment tools in patients admitted to hospital

L.1.3.1 General medical patients

L.1.3.1.1 Department of Health risk tool versus no risk tool

Figure 15: Mortality, VTE-related (time-point not reported)

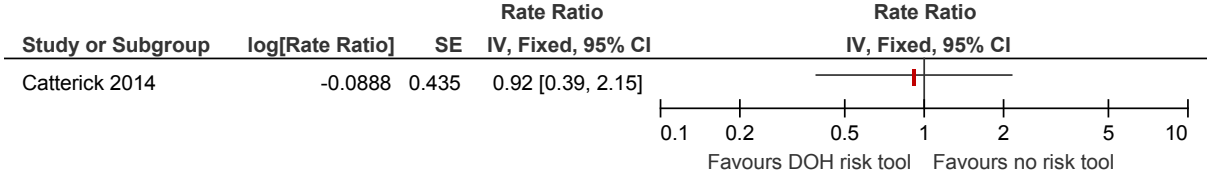


Figure 16: Readmission (30 days)

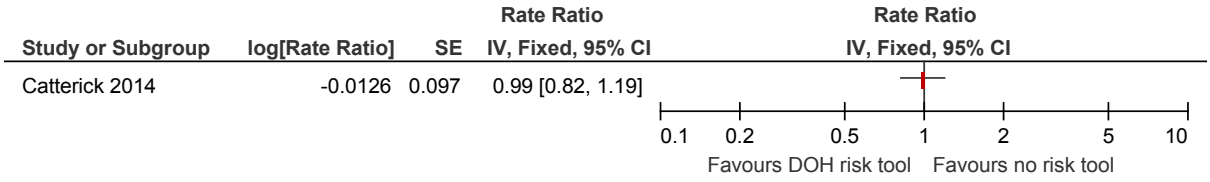
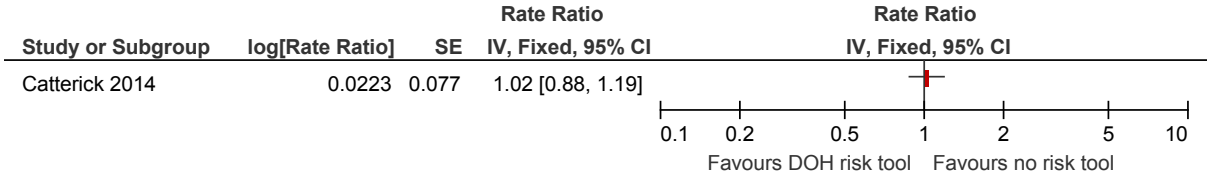


Figure 17: Readmission (90 days)



L.1.3.2 Department of Health risk tool: achieving >90% of admissions assessed using Department of Health risk tool versus achieving <90% assessed using risk tool

Figure 18: Mortality, VTE-related post-discharge (90 days)

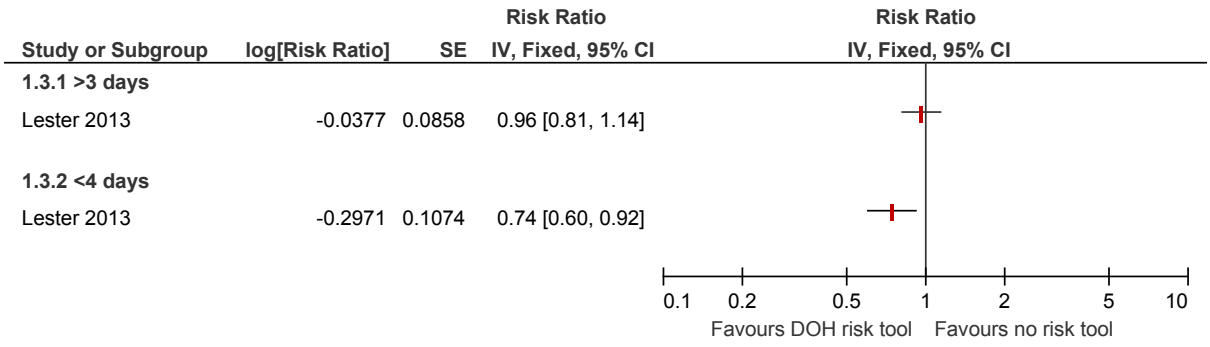


Figure 19: Mortality, primary VTE-related post-discharge (90 days)

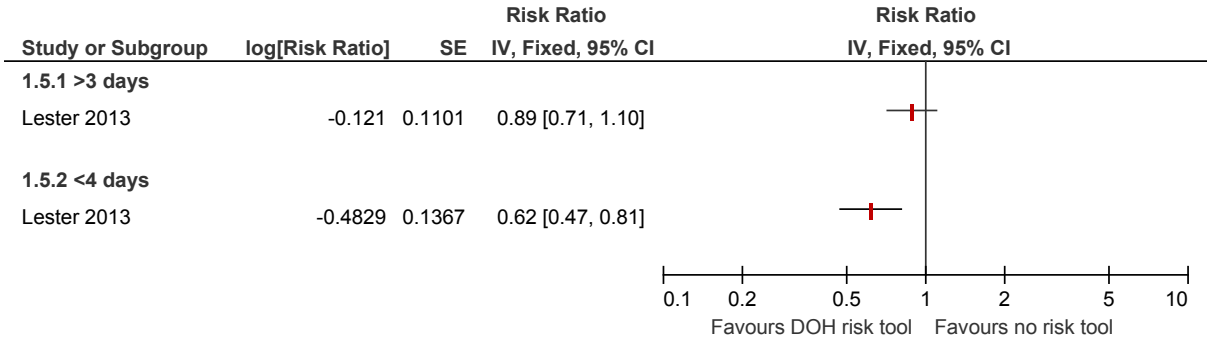


Figure 20: VTE (90 days)

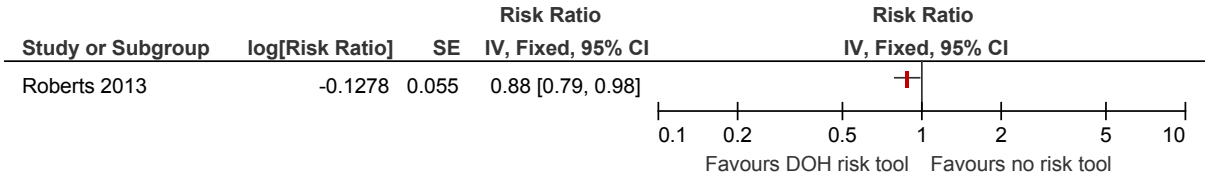


Figure 21: DVT (90 days)

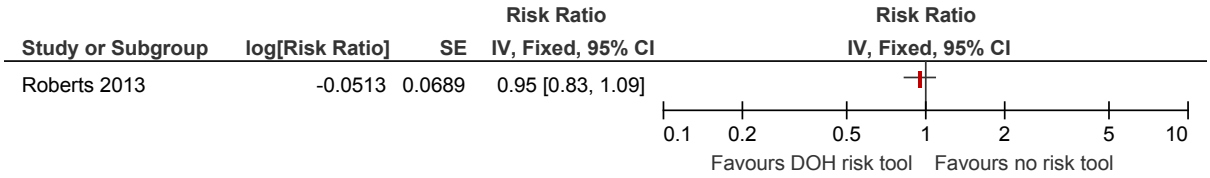
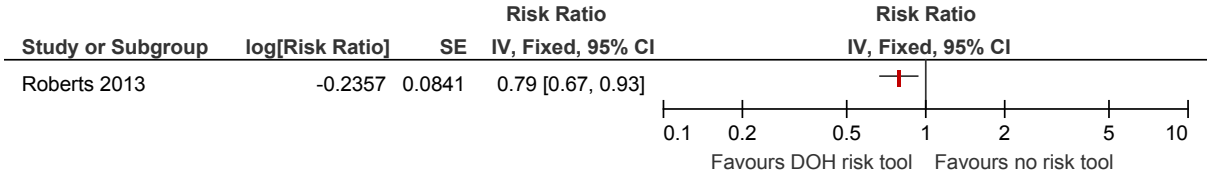


Figure 22: PE (90 days)



L.1.3.3 Padua prediction score versus no risk tool

Figure 23: All cause mortality (during hospital admission)

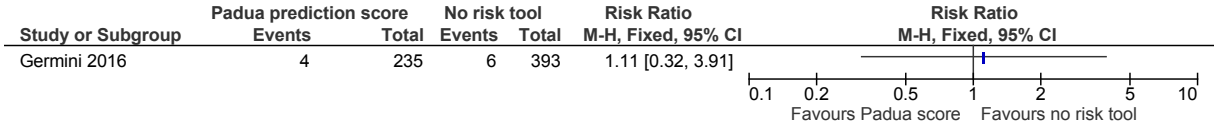


Figure 24: DVT (during hospital admission)

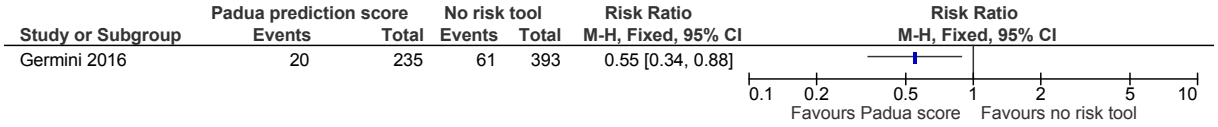


Figure 25: PE (during hospital admission)

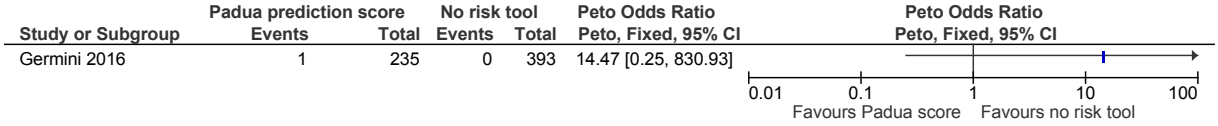


Figure 26: Fatal PE (during hospital admission)

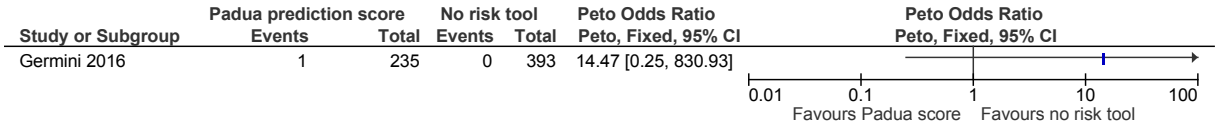
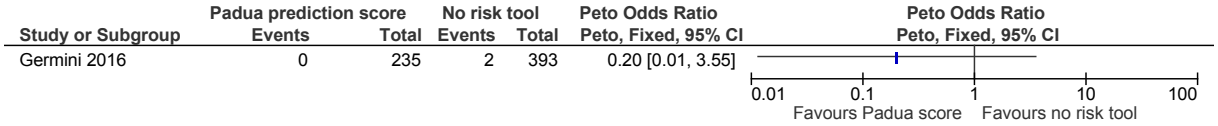


Figure 27: Major bleeding (during hospital admission)



L.1.3.4 Surgical patients

L.1.3.4.1 Caprini risk tool versus no risk tool

Figure 28: DVT (30 days)

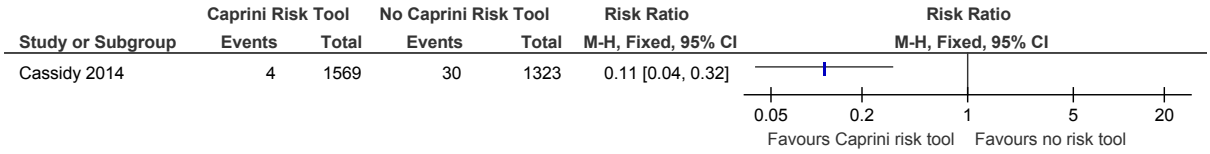
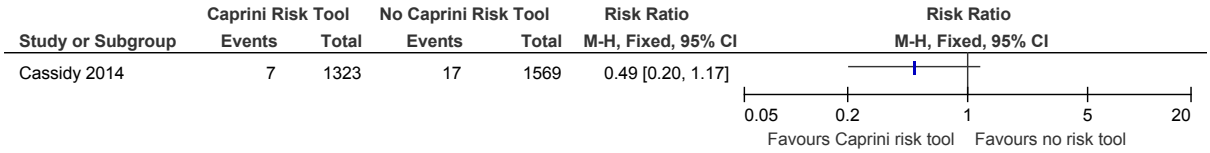


Figure 29: PE (30 days)



L.1.3.5 Department of Health risk tool: achieving > 90% of admissions assessed using Department of Health risk tool versus achieving < 90% assessed using risk tool

Figure 30: Mortality, VTE-related post-discharge (90 days)

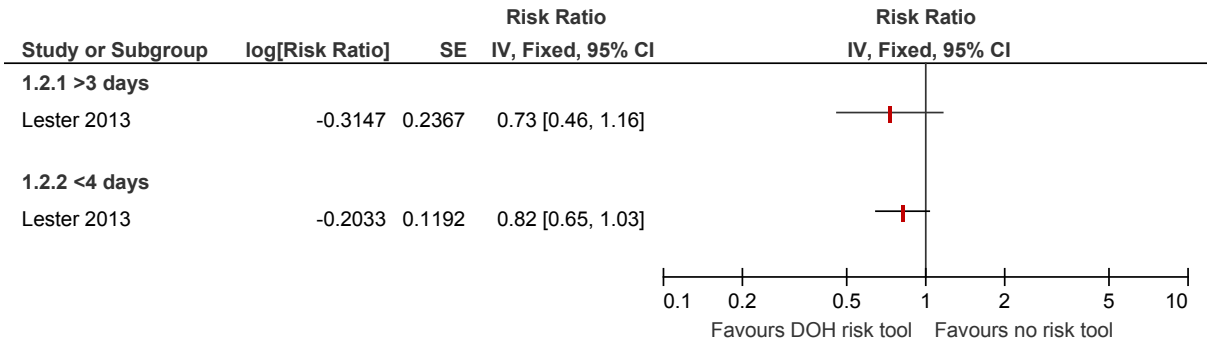
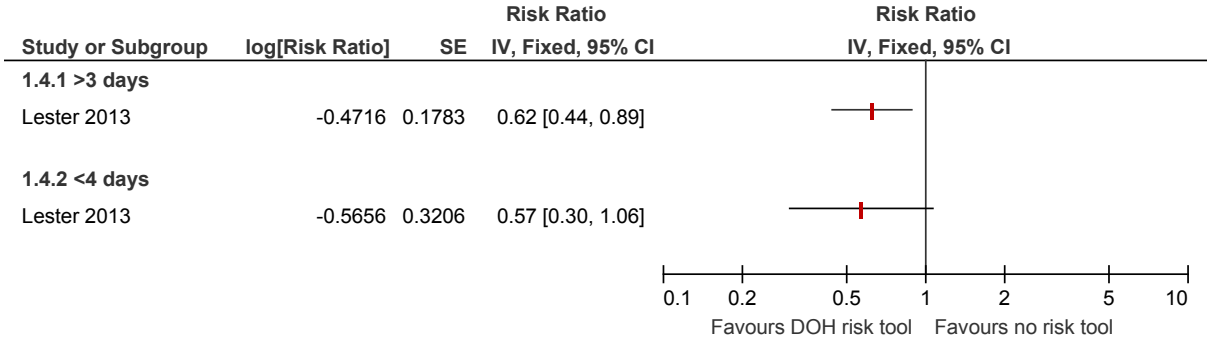


Figure 31: Mortality, primary VTE-related post-discharge (90 days)



L.2 Risk assessment for people having day procedures

L.2.1 VTE day procedures

L.2.1.1 Coupled sensitivity and specificity forest plots

L.2.1.1.1 People having cancer treatment

Figure 32: Sensitivity and specificity of Khorana score for predicting VTE in people with cancer

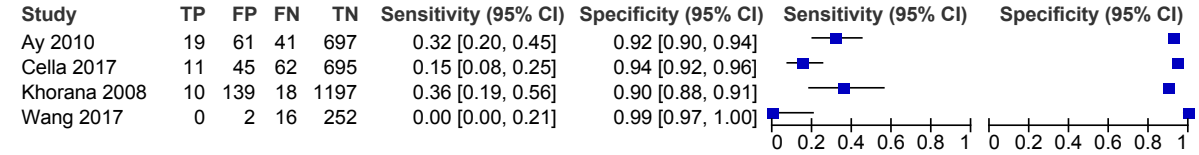
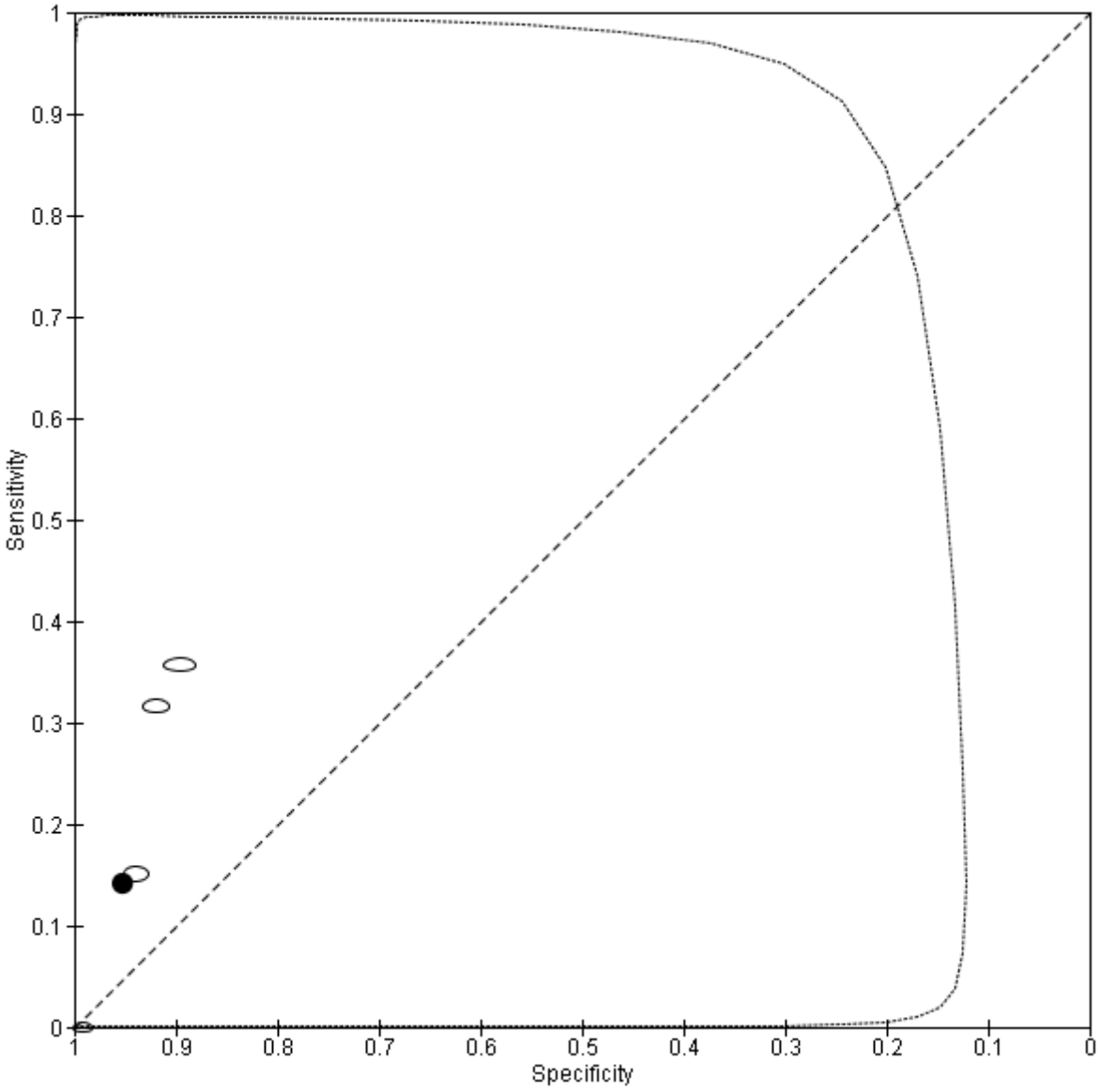


Figure 33: Summary ROC plot of sensitivity and specificity of Khorana score for predicting VTE in people with cancer.



L.2.2 Major bleeding day procedures

No relevant clinical studies identified.

L.2.3 Risk assessment tools in patients who are having day procedures (including surgery and chemotherapy) at hospital

No relevant clinical studies identified.

L.3 Reassessment

L.3.1 Reassessment of people who are admitted to hospital

No relevant clinical studies identified.

L.3.2 Reassessment of people who are having day procedures at hospital

No relevant clinical studies identified.

L.4 Risk assessment for pregnant women and women up to 6 weeks postpartum

L.4.1 VTE within 6 weeks postpartum

Figure 34: Sensitivity and specificity for the risk prediction model for identifying the top 1% (arbitrary cut-off) of pregnant and postpartum women at risk for VTE

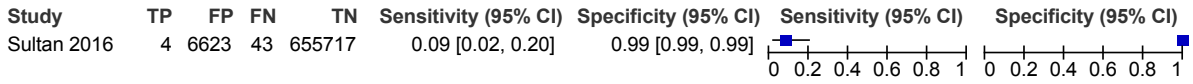


Figure 35: Sensitivity and specificity for the risk prediction model for identifying the top 5% (arbitrary cut-off) of pregnant and postpartum women at risk for VTE

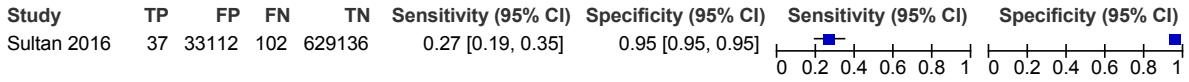


Figure 36: Sensitivity and specificity for the risk prediction model in pregnant and postpartum women for VTE at a cut-off of 6% (based on women given thromboprophylaxis according to according to 2011 Swedish SFOG national guidelines)

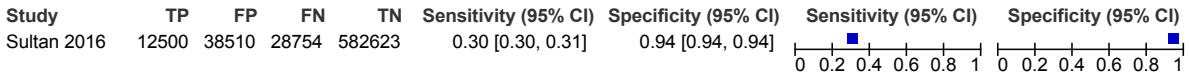


Figure 37: Sensitivity and specificity for the risk prediction model for identifying the top 10% (arbitrary cut-off) of pregnant and postpartum women at risk for VTE

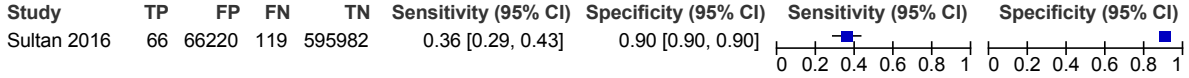


Figure 38: Sensitivity and specificity for the risk prediction model for identifying the top 20% (arbitrary cut-off) of pregnant and postpartum women at risk for VTE

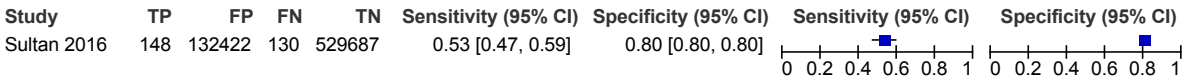


Figure 39: Sensitivity and specificity for the risk prediction model for identifying the top 25% (arbitrary cut-off) of pregnant and postpartum women at risk for VTE

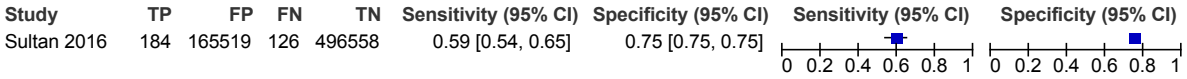
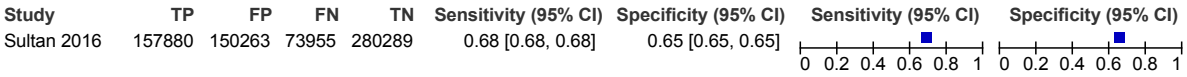


Figure 40: Sensitivity and specificity for the risk prediction model in pregnant and postpartum women for VTE at a cut-off of 35% (based on the proportion of women qualified for pharmacological thromboprophylaxis according to 2015 UK RCOG postnatal thromboprophylasxis guidelines, 2015)



L.5 Giving information to patients and planning for discharge

No relevant clinical studies identified.

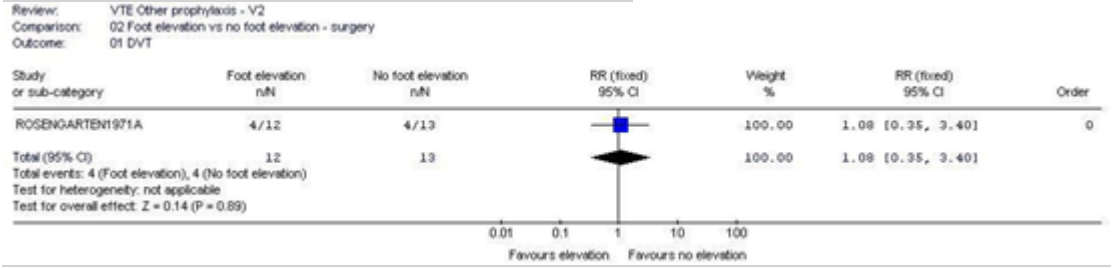
L.6 General VTE prevention for everyone in hospital

None

L.7 Nursing care: Early mobilisation and hydration

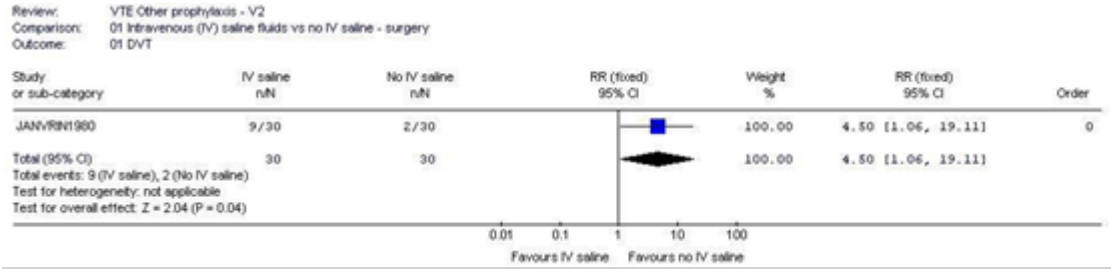
L.7.1 Foot elevation

Figure 41: Foot elevation vs no foot elevation - DVT



L.7.2 Hydration

Figure 42: IV saline vs no IV saline - DVT



L.8 Obesity

No relevant clinical studies identified.

L.9 People using antiplatelets

No relevant clinical studies identified.

L.10 People using anticoagulation therapy

L.10.1 LMWH (Bemiparin, 3500 IU) versus UFH (5000 IU)

Figure 43: Mortality (90 days)

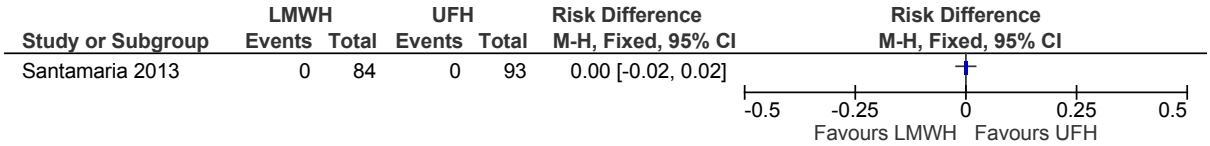
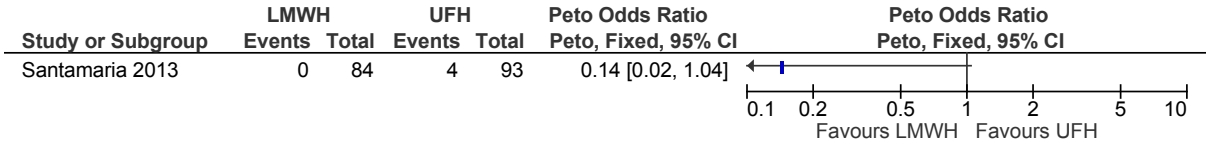


Figure 44: Major bleeding (90 days)



L.11 Acute coronary syndromes

No relevant clinical studies identified.

L.12 Acute stroke patients

L.12.1 AES (above knee) versus no prophylaxis

Figure 45: All-cause mortality (mean: 30 days)

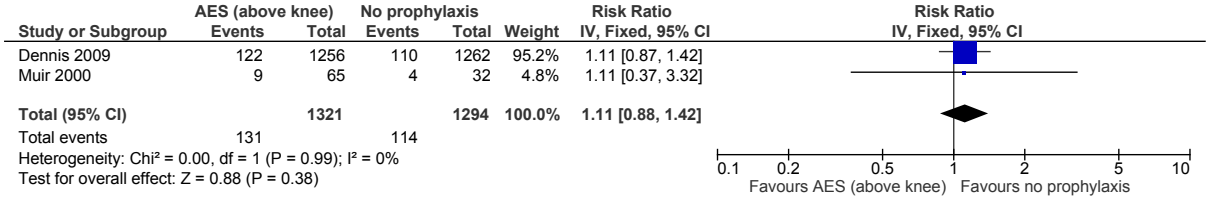


Figure 46: DVT (mean: 30 days)

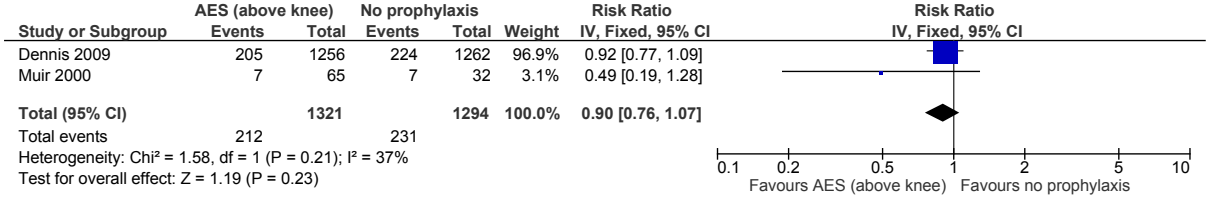


Figure 47: PE (mean: 30 days)

Study or Subgroup	AES (above knee) Events	Total	No prophylaxis Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Dennis 2009	13	1256	20	1262	100.0%	0.65 [0.33, 1.31]
Muir 2000	0	65	0	32		Not estimable
Total (95% CI)		**1321**		**1294**	**100.0%**	**0.65 [0.33, 1.31]**
Total events	13		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)

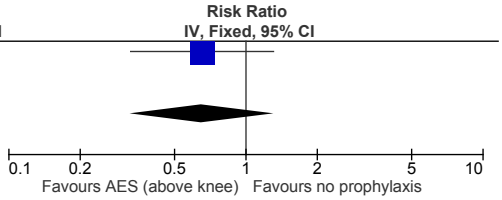


Figure 48: Fatal PE (30 days)

Study or Subgroup	AES (above knee) Events	Total	No prophylaxis Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Dennis 2009	1	1256	1	1262	1.00 [0.06, 16.07]

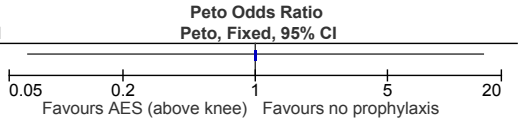


Figure 49: Technical complication (1) skin break (30 days)

Study or Subgroup	AES (above knee) Events	Total	No prophylaxis Events	Total	Risk Ratio IV, Fixed, 95% CI
Dennis 2009	64	1256	16	1262	4.02 [2.34, 6.91]

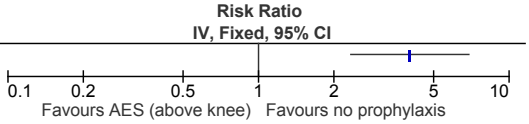
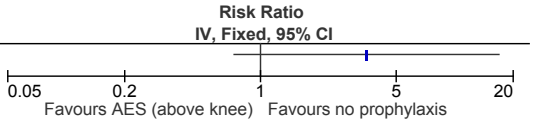


Figure 50: Technical complication (2) lower limb ischaemia or amputation (30 days)

Study or Subgroup	AES (above knee) Events	Total	No prophylaxis Events	Total	Risk Ratio IV, Fixed, 95% CI
Dennis 2009	7	1256	2	1262	3.52 [0.73, 16.90]



L.12.2 AES (thigh-length) versus AES (knee-length)

Figure 51: All-cause mortality (30 days)

Study or Subgroup	AES (thigh-length) Events	Total	AES (knee-length) Events	Total	Risk Ratio IV, Fixed, 95% CI
Dennis 2010	182	1552	174	1562	1.05 [0.87, 1.28]

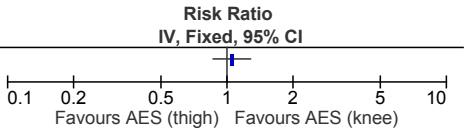


Figure 52: DVT (30 days)

Study or Subgroup	AES (thigh-length) Events	Total	AES (knee-length) Events	Total	Risk Ratio IV, Fixed, 95% CI
Dennis 2010	177	1552	211	1562	0.84 [0.70, 1.02]

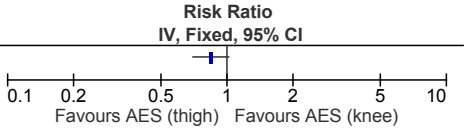


Figure 53: PE (30 days)

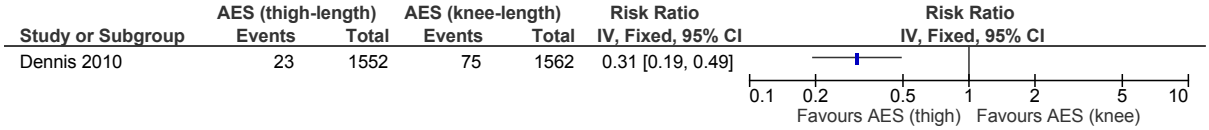


Figure 54: Technical complication (1) discontinued due to skin concerns (30 days)

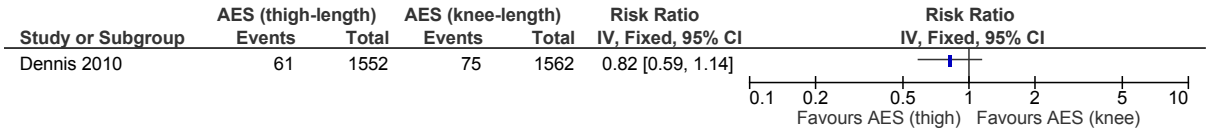
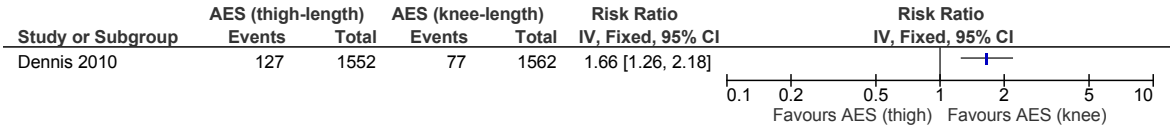


Figure 55: Technical complication(2) discontinued due to discomfort (30 days)



L.12.3 IPCD (full leg) versus no prophylaxis

Figure 56: All-cause mortality (mean: 30 days)

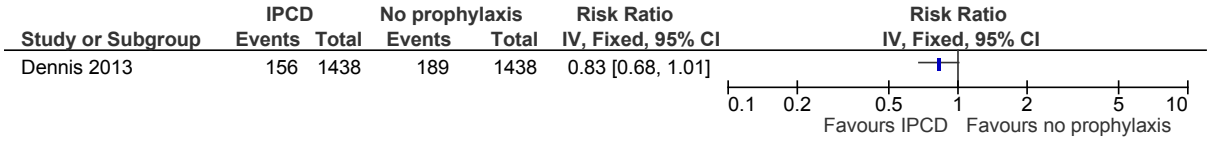


Figure 57: DVT (mean: 30 days)

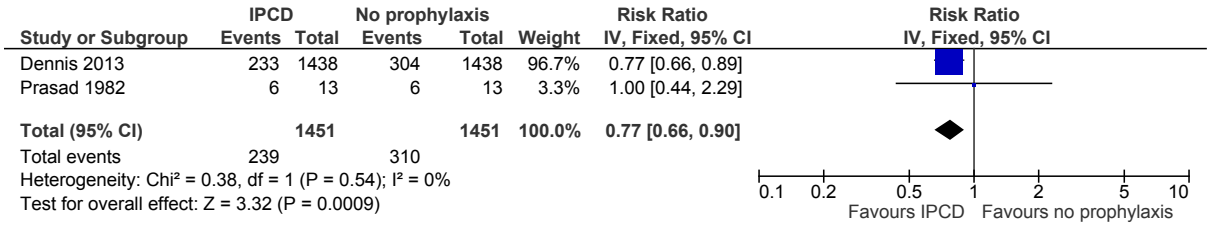


Figure 58: PE (mean: 30 days)

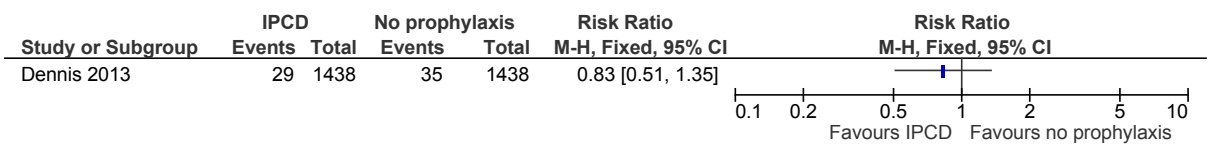
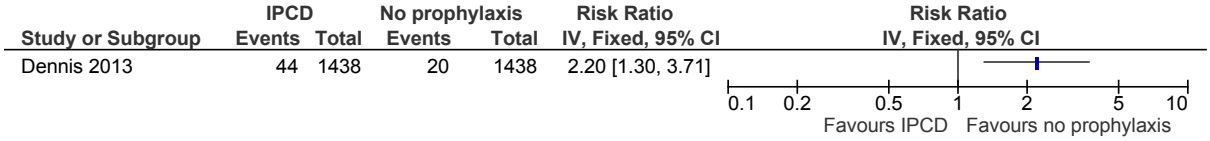


Figure 59: Technical complication (1) Skin breaks on legs (30 days)



L.12.4 IPCD + AES versus UFH + AES

Figure 60: All-cause mortality (22 days)

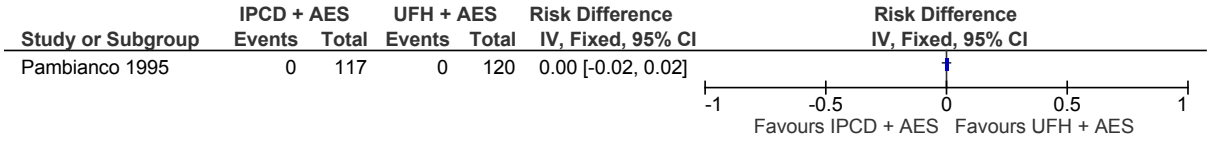
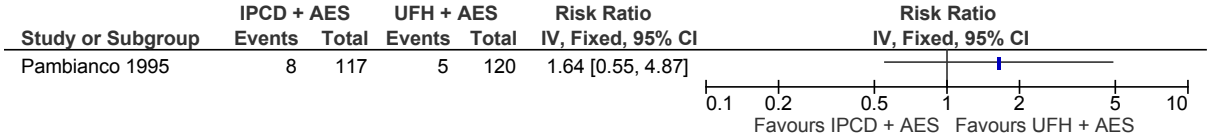


Figure 61: DVT (22 days)



L.12.5 IPCD + AES versus AES

Figure 62: All-cause mortality (90 days)

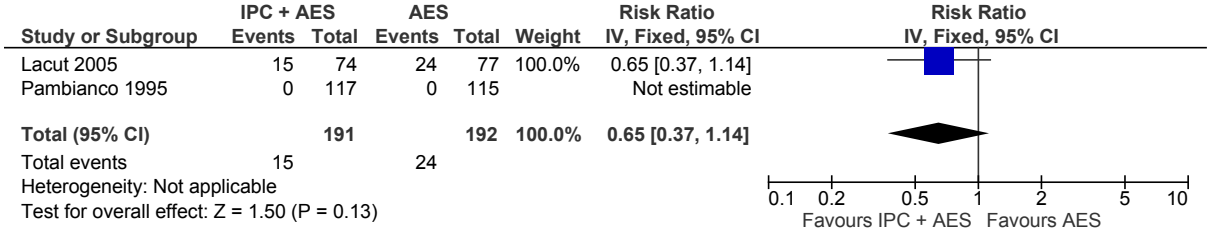
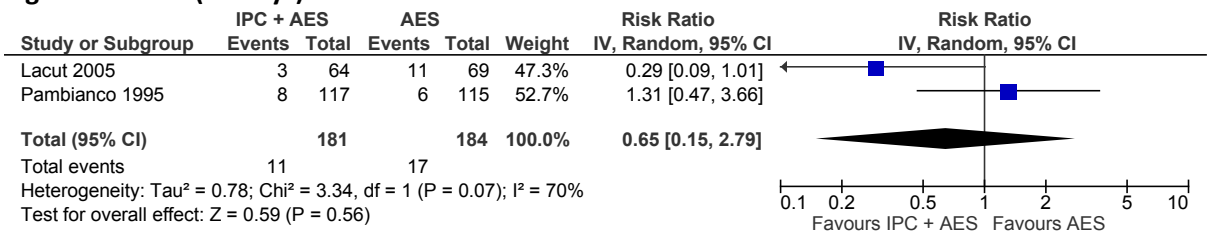


Figure 63: DVT (22 days)



L.12.6 UFH + AES versus AES

Figure 64: All-cause mortality (22 days)

Study or Subgroup	UFH + AES Events	UFH + AES Total	AES Events	AES Total	Risk Difference IV, Fixed, 95% CI
Pambianco 1995	0	120	0	115	0.00 [-0.02, 0.02]

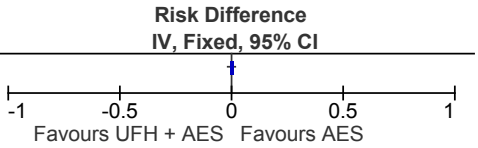
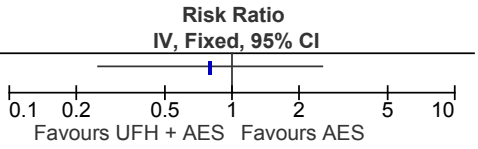


Figure 65: DVT (22 days)

Study or Subgroup	UFH + AES Events	UFH + AES Total	AES Events	AES Total	Risk Ratio IV, Fixed, 95% CI
Pambianco 1995	5	120	6	115	0.80 [0.25, 2.54]



L.12.7 UFH versus no prophylaxis

Figure 66: All-cause mortality (28 days)

Study or Subgroup	UFH Events	UFH Total	No prophylaxis Events	No prophylaxis Total	Weight	Risk Ratio IV, Fixed, 95% CI
McCarthy 1977	3	16	5	16	8.5%	0.60 [0.17, 2.10]
McCarthy 1986	31	144	53	161	91.5%	0.65 [0.45, 0.96]
Total (95% CI)		**160**		**177**	**100.0%**	**0.65 [0.45, 0.94]**
Total events	34		58			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)

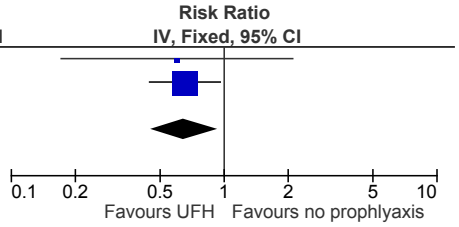
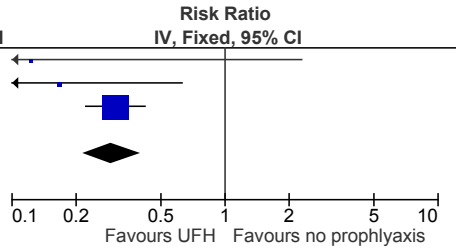


Figure 67: DVT (28 days)

Study or Subgroup	UFH Events	UFH Total	No prophylaxis Events	No prophylaxis Total	Weight	Risk Ratio IV, Fixed, 95% CI
Duke 1983	0	35	3	30	1.1%	0.12 [0.01, 2.29]
McCarthy 1977	2	16	12	16	5.4%	0.17 [0.04, 0.63]
McCarthy 1986	32	144	117	161	93.4%	0.31 [0.22, 0.42]
Total (95% CI)		**195**		**207**	**100.0%**	**0.29 [0.21, 0.40]**
Total events	34		132			

Heterogeneity: Chi² = 1.10, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 7.78 (P < 0.00001)



L.12.8 LMWH (standard dose; standard duration) versus no prophylaxis

Figure 68: All-cause mortality (14 days)

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Weight	Risk Ratio IV, Fixed, 95% CI
Prins 1989	9	30	4	30	79.8%	2.25 [0.78, 6.52]
Sandset 1990	5	52	1	51	20.2%	4.90 [0.59, 40.53]
Total (95% CI)		**82**		**81**	**100.0%**	**2.63 [1.02, 6.81]**
Total events	14		5			

Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)

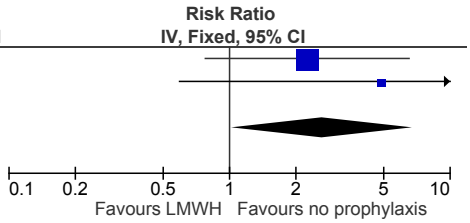


Figure 69: DVT (symptomatic and asymptomatic) (14 days)

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Weight	Risk Ratio IV, Random, 95% CI
Prins 1989	6	27	15	30	44.5%	0.44 [0.20, 0.98]
Sandset 1990	15	42	17	50	55.5%	1.05 [0.60, 1.84]
Total (95% CI)		**69**		**80**	**100.0%**	**0.72 [0.31, 1.66]**
Total events	21		32			

Heterogeneity: Tau² = 0.25; Chi² = 3.02, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 0.78 (P = 0.44)

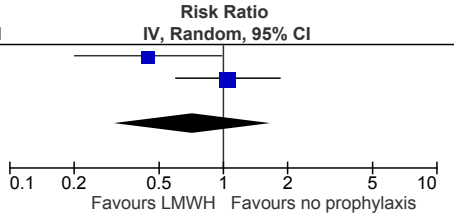


Figure 70: PE (14 days)

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio IV, Fixed, 95% CI
Prins 1989	1	30	2	30	0.50 [0.05, 5.22]

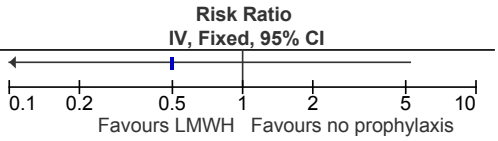


Figure 71: Major bleeding (14 days)

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Risk Difference IV, Fixed, 95% CI
Sandset 1990	0	52	0	51	0.00 [-0.04, 0.04]

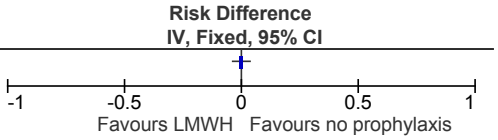


Figure 72: Fatal PE (14 days)

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Peto Odds Ratio Peto, Fixed, 95% CI
Sandset 1990	0	52	1	51	0.13 [0.00, 6.69]

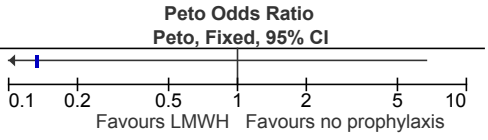
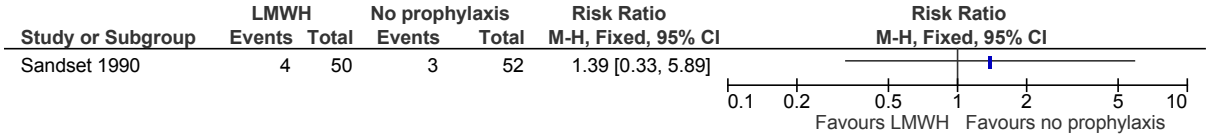


Figure 73: Haemorrphagic transformation (15 days)



L.12.9 LMWH (high dose; standard duration) versus aspirin

Figure 74: All-cause mortality (90 days)

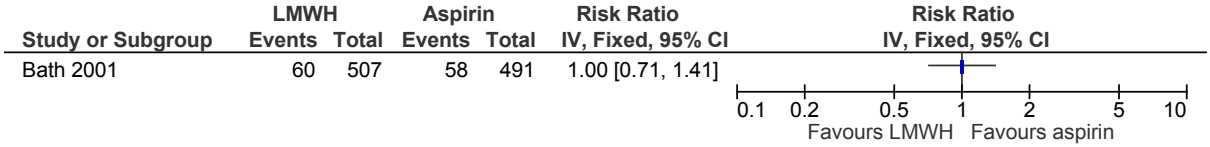


Figure 75: DVT (symptomatic and asymptomatic) (15 days)

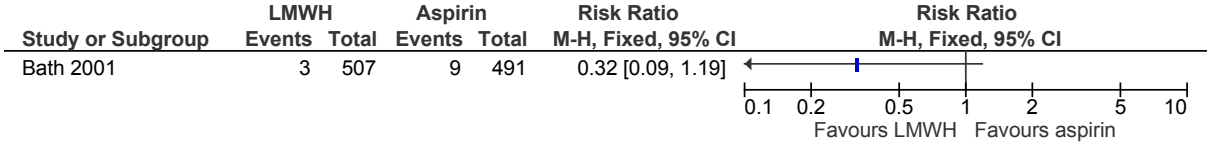


Figure 76: PE (15 days)

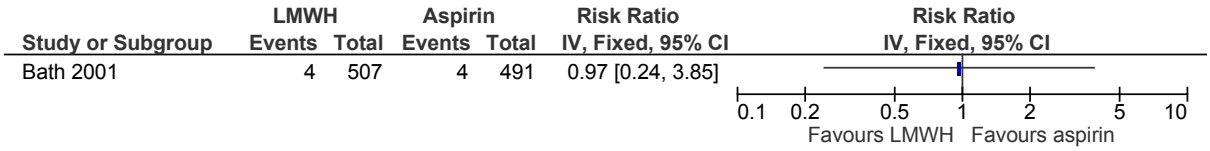


Figure 77: Major bleeding (15 days)

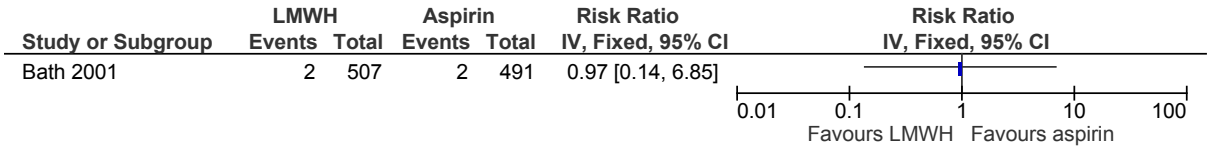


Figure 78: Modified Rankin Scale (90 days) (patients with score 0-2) (higher score is worse)

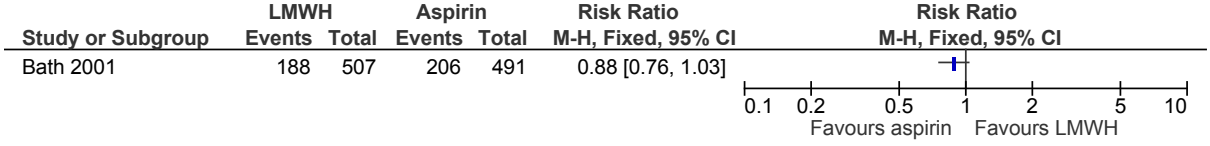


Figure 79: Barthel Index (90 days) (patients with score 60-100) (higher score is better)

Study or Subgroup	LMWH Events	LMWH Total	Aspirin Events	Aspirin Total	Risk Ratio M-H, Fixed, 95% CI
Bath 2001	313	507	320	491	0.95 [0.86, 1.04]

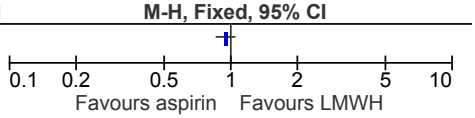
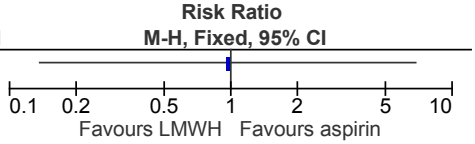


Figure 80: Heparin-induced thrombocytopenia (15 days)

Study or Subgroup	LMWH Events	LMWH Total	Aspirin Events	Aspirin Total	Risk Ratio M-H, Fixed, 95% CI
Bath 2001	2	507	2	491	0.97 [0.14, 6.85]



L.12.10 LMWH (standard dose; standard duration) versus UFH

Figure 81: All-cause mortality (90 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio IV, Fixed, 95% CI
Diener 2006	21	272	15	273	11.4%	1.41 [0.74, 2.67]
Hillbom 2002	21	106	28	106	18.9%	0.75 [0.46, 1.23]
Sherman 2007	100	884	103	878	69.8%	0.96 [0.74, 1.25]
Total (95% CI)		**1262**		**1257**	**100.0%**	**0.96 [0.77, 1.19]**
Total events	142		146			

Heterogeneity: Chi² = 2.30, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 0.37 (P = 0.71)

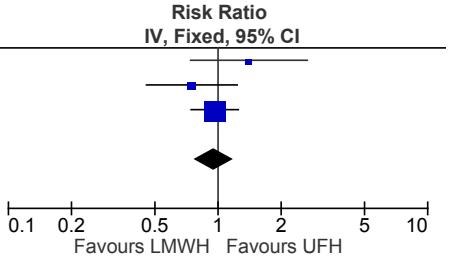


Figure 82: DVT (mean: 14 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio IV, Fixed, 95% CI
Hillbom 2002	14	76	24	72	19.2%	0.55 [0.31, 0.98]
Sherman 2007	67	666	118	669	80.8%	0.57 [0.43, 0.75]
Total (95% CI)		**742**		**741**	**100.0%**	**0.57 [0.44, 0.73]**
Total events	81		142			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 4.42 (P < 0.00001)

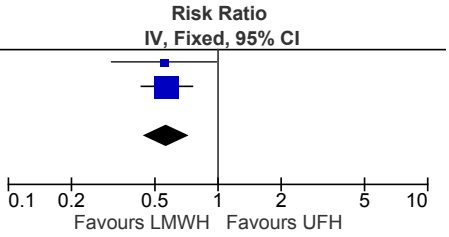


Figure 83: PE (mean: 14 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio IV, Fixed, 95% CI
Diener 2006	0	272	1	273	14.4%	0.33 [0.01, 8.18]
Hillbom 2002	2	106	4	106	52.5%	0.50 [0.09, 2.67]
Sherman 2007	1	666	6	669	33.0%	0.17 [0.02, 1.39]
Total (95% CI)		**1044**		**1048**	**100.0%**	**0.33 [0.10, 1.11]**
Total events	3		11			

Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)

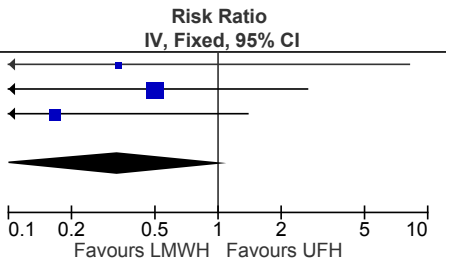


Figure 84: Major bleeding (mean: 14 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio IV, Fixed, 95% CI
Diener 2006	3	272	5	273	30.7%	0.60 [0.15, 2.50]
Hillbom 2002	1	106	0	106	6.1%	3.00 [0.12, 72.82]
Sherman 2007	11	877	6	872	63.2%	1.82 [0.68, 4.91]
Total (95% CI)		**1255**		**1251**	**100.0%**	**1.34 [0.61, 2.94]**
Total events	15		11			

Heterogeneity: Chi² = 1.83, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

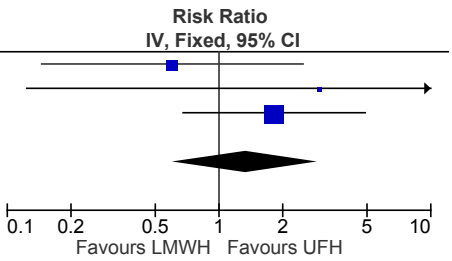


Figure 85: Fatal PE (mean: 14 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Diener 2006	0	272	1	273	14.4%	0.14 [0.00, 6.85]
Hillbom 2002	1	106	2	106	42.7%	0.51 [0.05, 4.96]
Sherman 2007	1	666	2	669	43.0%	0.52 [0.05, 4.96]
Total (95% CI)		**1044**		**1048**	**100.0%**	**0.42 [0.10, 1.87]**
Total events	2		5			

Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)

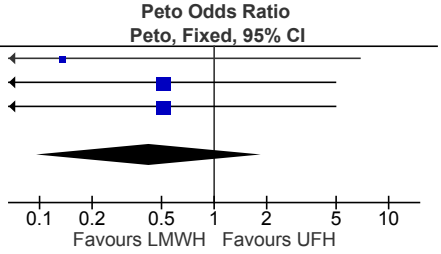


Figure 86: Clinically relevant non-major bleeding (mean: 14 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio IV, Fixed, 95% CI
Hillbom 2002	5	106	6	106	10.9%	0.83 [0.26, 2.65]
Sherman 2007	42	877	48	872	89.1%	0.87 [0.58, 1.30]
Total (95% CI)		**983**		**978**	**100.0%**	**0.87 [0.59, 1.27]**
Total events	47		54			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)

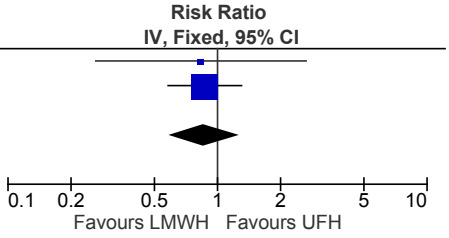


Figure 87: Heparin-induced thrombocytopenia (time-point unclear)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Peto Odds Ratio Peto, Fixed, 95% CI
Diener 2006	1	272	2	273	0.51 [0.05, 4.96]

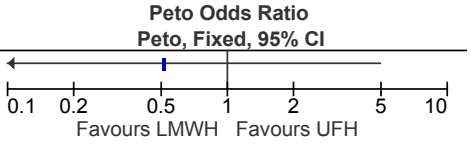
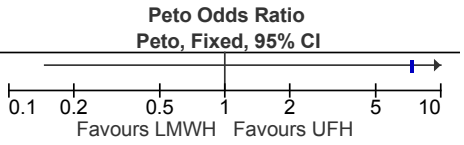


Figure 88: Neurological bleeds haemorrhagic transformation only (mean:14 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Peto Odds Ratio Peto, Fixed, 95% CI
Hillbom 2002	1	106	0	106	7.39 [0.15, 372.38]



L.13 Acutely ill medical patients

L.13.1 LMWH (standard dose; standard duration) versus no prophylaxis

Figure 89: All-cause mortality (time-point not reported/90 days)

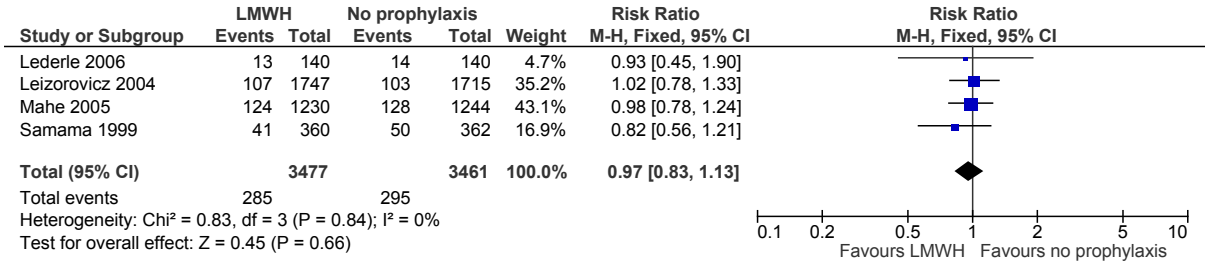


Figure 90: DVT (symptomatic and asymptomatic) (time-point not reported)

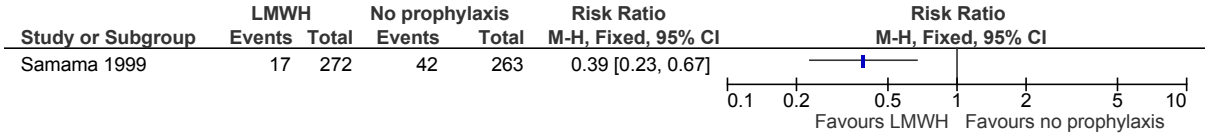


Figure 91: PE (time-point not reported/90 days)

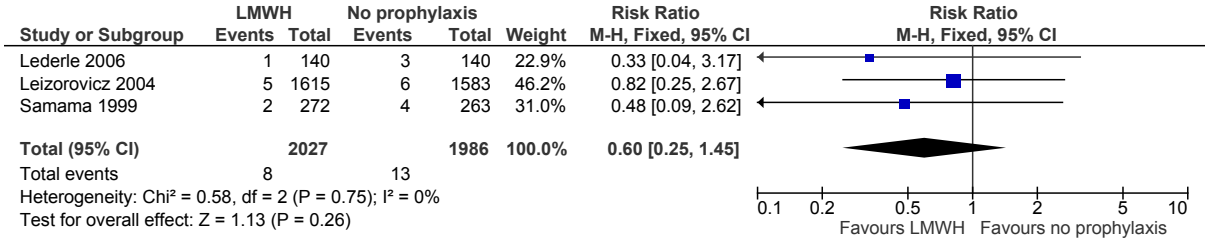


Figure 92: Major bleeding (time-point not reported)

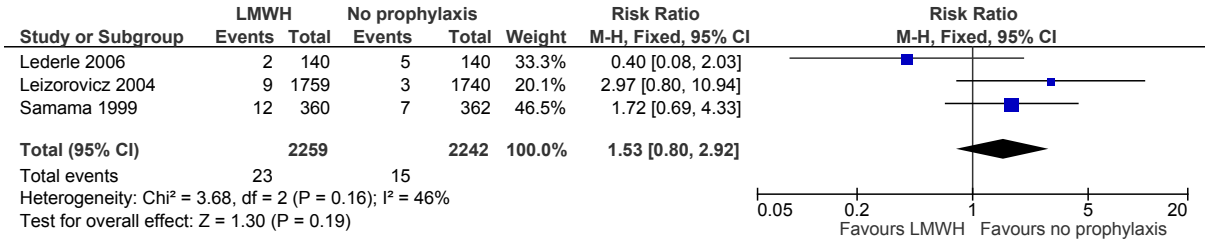


Figure 93: Fatal PE (time-point not reported/90 days)

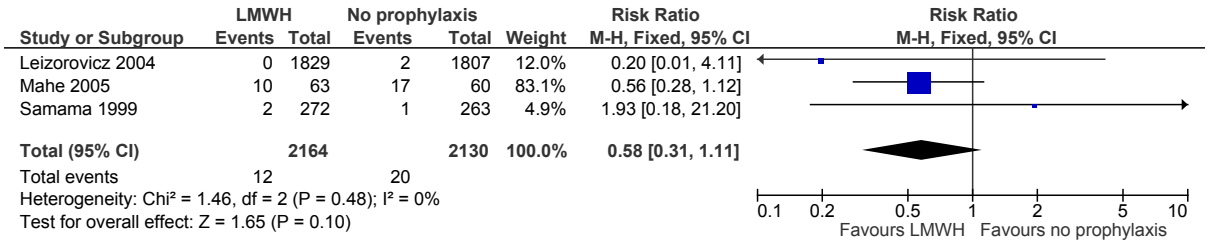
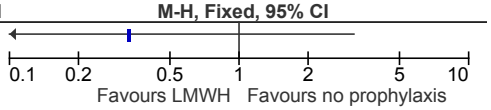


Figure 94: Heparin-induced thrombocytopenia (time-point not reported)

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Lederle 2006	1	140	3	140	0.33 [0.04, 3.17]



L.13.2 LMWH (high dose; standard duration) versus no prophylaxis

Figure 95: All-cause mortality (10 days)

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Lederle 2006	1	140	3	140	0.33 [0.04, 3.17]

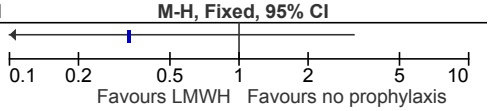


Figure 96: DVT (symptomatic and asymptomatic) (10 days)

Study or Subgroup	LMWH (high) Events	LMWH (high) Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Dahan 1986	4	132	12	131	0.33 [0.11, 1.00]

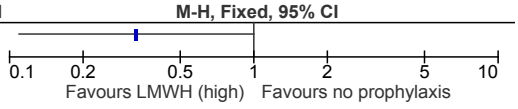
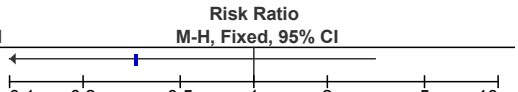


Figure 97: Fatal PE (10 days)

Study or Subgroup	LMWH (high) Events	LMWH (high) Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Dahan 1986	1	132	3	131	0.33 [0.03, 3.14]



L.13.3 LMWH (low dose; standard duration) versus no prophylaxis

Figure 98: All-cause mortality (110 days)

Study or Subgroup	LMWH (low) Events	LMWH (low) Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Samama 1999	51	351	50	362	1.05 [0.73, 1.51]

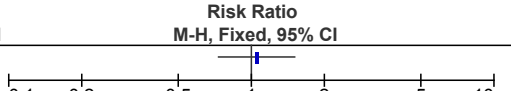


Figure 99: DVT (symptomatic and asymptomatic) (110 days)

Study or Subgroup	LMWH (low) Events	LMWH (low) Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Samama 1999	44	263	42	263	1.05 [0.71, 1.54]

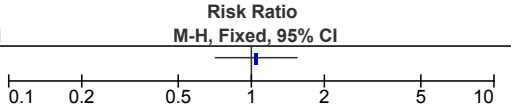


Figure 100: PE (110 days)

Study or Subgroup	LMWH (low) Events	Total	No prophylaxis Events	Total	Risk Ratio M-H, Fixed, 95% CI
Samama 1999	1	263	3	263	0.33 [0.03, 3.18]

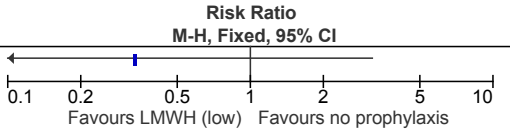


Figure 101: Major bleeding (14 days)

Study or Subgroup	LMWH (low) Events	Total	No prophylaxis Events	Total	Risk Ratio M-H, Fixed, 95% CI
Samama 1999	4	351	7	362	0.59 [0.17, 2.00]

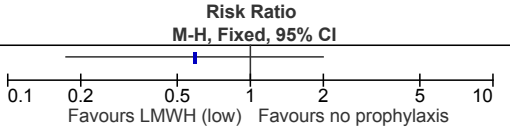
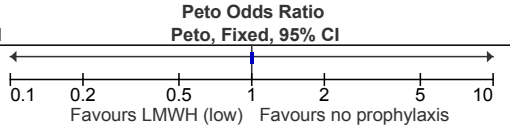


Figure 102: Fatal PE (110 days)

Study or Subgroup	LMWH (low) Events	Total	No prophylaxis Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Samama 1999	1	263	1	263	1.00 [0.06, 16.03]



L.13.4 LMWH (high dose; standard duration) versus LMWH (standard dose; standard duration)

Figure 103: All-cause mortality (14 days)

Study or Subgroup	LMWH (high dose) Events	Total	LMWH (standard dose) Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Miranda 2017	0	46	1	45	0.13 [0.00, 6.67]

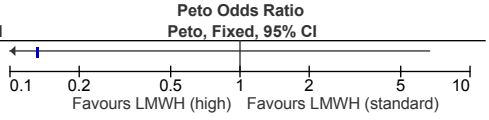


Figure 104: Major bleeding (14 days)

Study or Subgroup	LMWH (high dose) Events	Total	LMWH (standard dose) Events	Total	Risk Difference M-H, Fixed, 95% CI
Miranda 2017	0	46	0	45	0.00 [-0.04, 0.04]

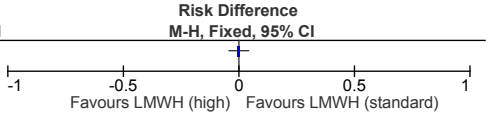
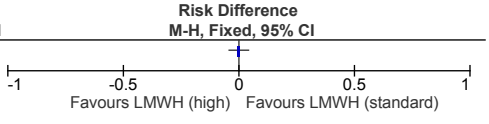


Figure 105: Heparin-induced thrombocytopenia (14 days)

Study or Subgroup	LMWH (high dose) Events	Total	LMWH (standard dose) Events	Total	Risk Difference M-H, Fixed, 95% CI
Miranda 2017	0	46	0	45	0.00 [-0.04, 0.04]



L.13.5 LMWH (standard dose; standard duration) versus LMWH (low dose; standard duration)

Figure 106: All-cause mortality (110 days)

Study or Subgroup	LMWH (standard) Events	Total	LMWH (low) Events	Total	Risk Ratio M-H, Fixed, 95% CI
Samama 1999	41	360	51	351	0.78 [0.53, 1.15]

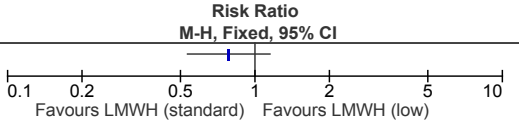


Figure 107: DVT (symptomatic and asymptomatic) (110 days)

Study or Subgroup	LMWH (standard) Events	Total	LMWH (low) Events	Total	Risk Ratio M-H, Fixed, 95% CI
Samama 1999	17	272	44	263	0.37 [0.22, 0.64]

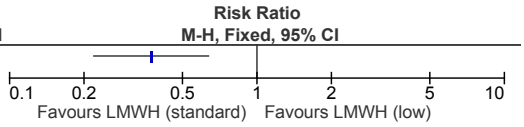


Figure 108: PE (110 days)

Study or Subgroup	LMWH (standard) Events	Total	LMWH (low) Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Samama 1999	0	272	1	263	0.13 [0.00, 6.59]

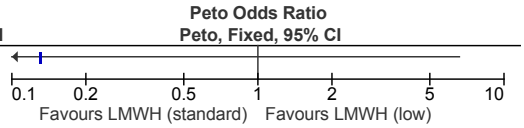


Figure 109: Major bleeding (14 days)

Study or Subgroup	LMWH (standard) Events	Total	LMWH (low) Events	Total	Risk Ratio M-H, Fixed, 95% CI
Samama 1999	6	360	1	351	5.85 [0.71, 48.34]

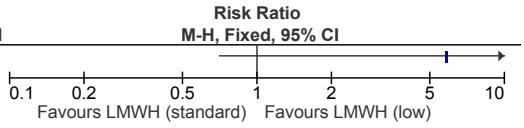
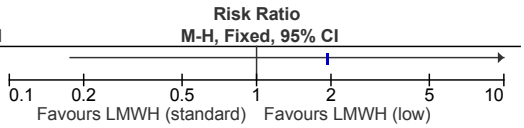


Figure 110: Fatal PE (110 days)

Study or Subgroup	LMWH (standard) Events	Total	LMWH (low) Events	Total	Risk Ratio M-H, Fixed, 95% CI
Samama 1999	2	272	1	263	1.93 [0.18, 21.20]



L.13.6 LMWH (extended duration; standard dose) versus LMWH (standard duration; standard dose)

Figure 111: All-cause mortality (90 days)

Study or Subgroup	LMWH (extended) Events	Total	LMWH (standard) Events	Total	Risk Ratio M-H, Fixed, 95% CI
Hull 2010	105	2159	105	2176	1.01 [0.77, 1.31]

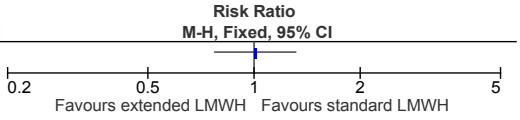


Figure 112: PE (90 days)

Study or Subgroup	LMWH (extended) Events	Total	LMWH (standard) Events	Total	Risk Ratio M-H, Fixed, 95% CI
Hull 2010	3	1818	7	1867	0.44 [0.11, 1.70]

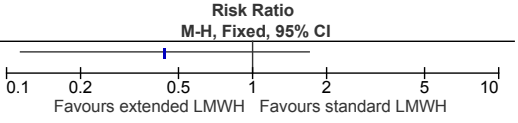
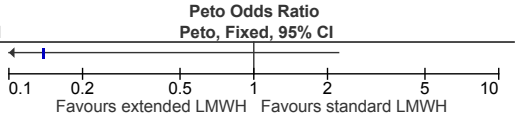


Figure 113: Fatal PE (90 days)

Study or Subgroup	LMWH (extended) Events	Total	LMWH (standard) Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Hull 2010	0	1818	2	1867	0.14 [0.01, 2.22]



L.13.7 LMWH (standard dose; standard duration) + AES versus AES

Figure 114: All-cause mortality (90 days)

Study or Subgroup	LMWH + AES Events	Total	AES Events	Total	Risk Ratio M-H, Fixed, 95% CI
Kakkar 2011	348	4171	355	4136	0.97 [0.84, 1.12]

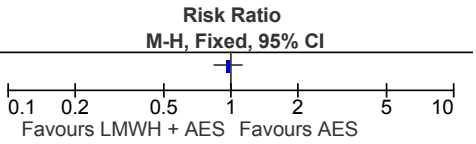


Figure 115: Major bleeding (8 days)

Study or Subgroup	LMWH + AES Events	Total	AES Events	Total	Risk Ratio M-H, Fixed, 95% CI
Kakkar 2011	16	4171	11	4136	1.44 [0.67, 3.10]

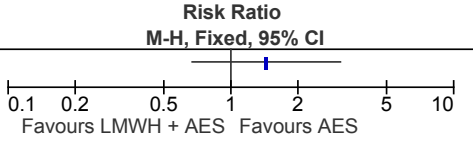
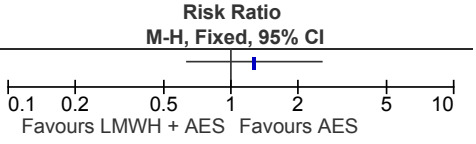


Figure 116: Clinically relevant non-major bleeding (8 days)

Study or Subgroup	LMWH + AES Events	Total	AES Events	Total	Risk Ratio M-H, Fixed, 95% CI
Kakkar 2011	18	4171	14	4136	1.27 [0.63, 2.56]



L.13.8 LMWH (standard dose; standard duration) versus UFH

Figure 117: All-cause mortality (8-90 days)

Study or Subgroup	LMWH Events	Total	UFH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Harenberg 1996	23	810	9	780	18.6%	2.46 [1.15, 5.28]
Kleber 2003	9	332	15	333	17.4%	0.60 [0.27, 1.36]
Lechler 1996	7	477	11	482	14.6%	0.64 [0.25, 1.64]
Riess 2010	66	1488	72	1459	33.2%	0.90 [0.65, 1.25]
Schellong 2010	8	163	12	172	16.1%	0.70 [0.30, 1.68]
Total (95% CI)		**3270**		**3226**	**100.0%**	**0.93 [0.59, 1.45]**
Total events	113		119			

Heterogeneity: Tau² = 0.13; Chi² = 8.37, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 0.34 (P = 0.74)

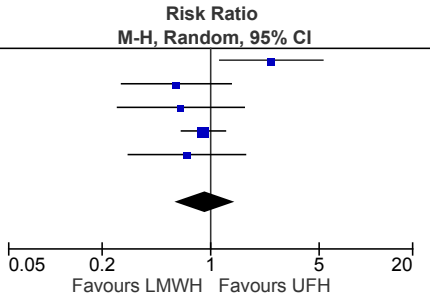


Figure 118: DVT (symptomatic and asymptomatic) (8-90 days)

Study or Subgroup	LMWH Events	Total	UFH Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kleber 2003	19	239	22	212	46.0%	0.77 [0.43, 1.38]
Lechler 1996	1	442	4	443	7.9%	0.25 [0.03, 2.23]
Schellong 2010	10	103	23	100	46.1%	0.42 [0.21, 0.84]
Total (95% CI)		**784**		**755**	**100.0%**	**0.57 [0.37, 0.87]**
Total events	30		49			

Heterogeneity: Chi² = 2.25, df = 2 (P = 0.32); I² = 11%
Test for overall effect: Z = 2.58 (P = 0.010)

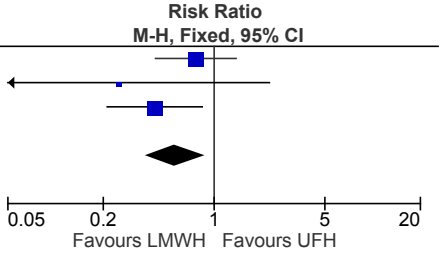


Figure 119: PE (8 - 90 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Harenberg 1996	3	810	3	780	31.6%	0.96 [0.19, 4.78]
Kleber 2003	1	239	0	212	5.3%	6.60 [0.13, 334.96]
Lechler 1996	0	442	4	443	21.1%	0.13 [0.02, 0.96]
Riess 2010	3	1483	2	1454	26.4%	1.46 [0.25, 8.46]
Schellong 2010	1	103	2	100	15.7%	0.49 [0.05, 4.81]
Total (95% CI)		**3077**		**2989**	**100.0%**	**0.71 [0.29, 1.74]**
Total events	8		11			

Heterogeneity: Chi² = 4.88, df = 4 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.75 (P = 0.45)

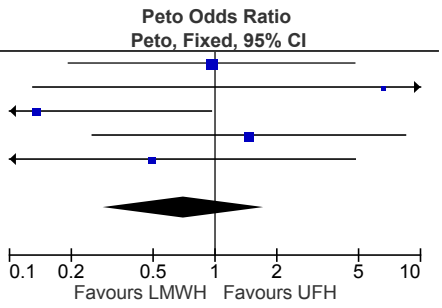


Figure 120: Major bleeding (8- 90 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio IV, Fixed, 95% CI
Harenberg 1996	5	810	4	780	25.1%	1.20 [0.32, 4.47]
Ishi 2013	0	44	4	48	5.2%	0.12 [0.01, 2.18]
Kleber 2003	1	332	1	333	5.6%	1.00 [0.06, 15.97]
Lechler 1996	2	477	7	482	17.6%	0.29 [0.06, 1.38]
Riess 2010	7	1624	10	1615	46.5%	0.70 [0.27, 1.82]
Total (95% CI)		**3287**		**3258**	**100.0%**	**0.64 [0.33, 1.23]**
Total events	15		26			

Heterogeneity: Chi² = 3.29, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)

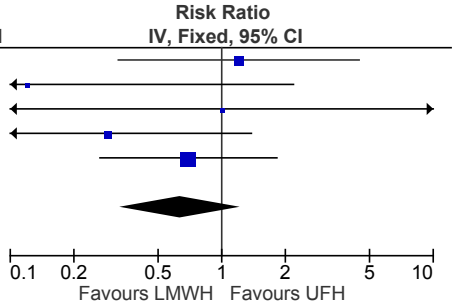


Figure 121: Fatal PE (time-point not reported)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Harenberg 1996	1	810	0	780	50.1%	7.12 [0.14, 359.10]
Kleber 2003	0	239	1	212	49.9%	0.12 [0.00, 6.05]
Total (95% CI)		**1049**		**992**	**100.0%**	**0.92 [0.06, 14.82]**
Total events	1		1			

Heterogeneity: Chi² = 2.09, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 0.06 (P = 0.96)

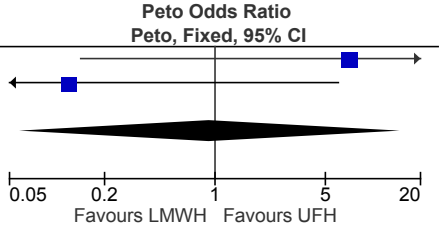
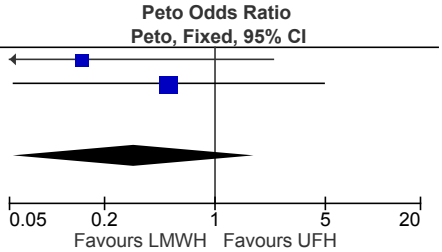


Figure 122: Heparin-induced thrombocytopenia (90 days)

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ishi 2013	0	44	2	48	39.7%	0.14 [0.01, 2.34]
Riess 2010	1	1624	2	1615	60.3%	0.51 [0.05, 4.91]
Schellong 2010	0	163	0	172		Not estimable
Total (95% CI)		**1831**		**1835**	**100.0%**	**0.31 [0.05, 1.79]**
Total events	1		4			

Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)



L.13.9 LMWH (standard dose; standard duration) versus apixaban

Figure 123: All-cause mortality (30 days)

Study or Subgroup	Favours LMWH Events	Total	Apixaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Goldhaber 2011	3	3273	2	3255	1.49 [0.25, 8.92]

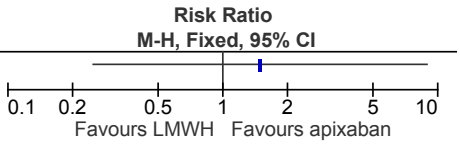


Figure 124: PE (30 days)

Study or Subgroup	LMWH Events	Total	Apixaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Goldhaber 2011	8	3266	7	3251	1.14 [0.41, 3.13]

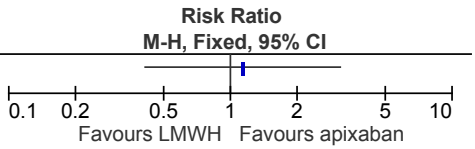


Figure 125: Major bleeding (including fatal bleeding) (30 days)

Study or Subgroup	LMWH Events	Total	Apixaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Goldhaber 2011	6	3217	15	3184	0.40 [0.15, 1.02]

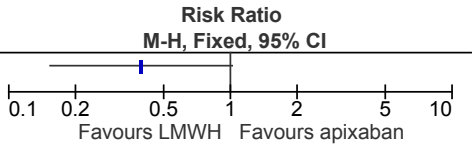
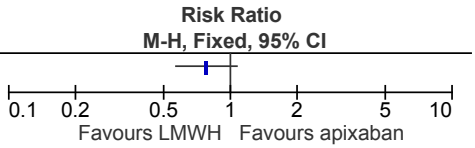


Figure 126: Major bleeding plus clinically non-major bleeding (30 days)

Study or Subgroup	LMWH Events	Total	Apixaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Goldhaber 2011	67	3217	85	3184	0.78 [0.57, 1.07]



L.13.10 Rivaroxaban versus LMWH (standard dose; standard duration)

Figure 127: All-cause mortality (35 days)

Study or Subgroup	Rivaroxaban Events	Total	LMWH Events	Total	Risk Ratio M-H, Fixed, 95% CI
Cohen 2013	159	3096	153	3169	1.06 [0.86, 1.32]

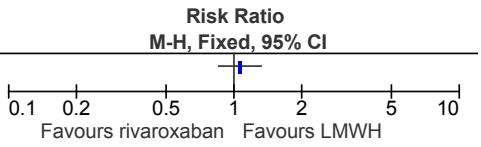


Figure 128: DVT (symptomatic and asymptomatic) (35 days)

Study or Subgroup	Rivaroxaban Events	Total	LMWH Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cohen 2013	116	2967	148	3057		0.81 [0.64, 1.02]

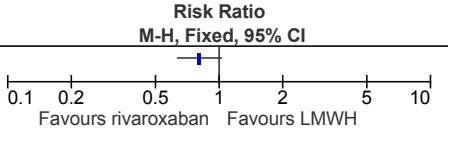


Figure 129: PE (35 days)

Study or Subgroup	Rivaroxaban Events	Total	LMWH Events	Total	Risk Ratio M-H, Fixed, 95% CI
Cohen 2013	10	2967	14	3057	0.74 [0.33, 1.65]

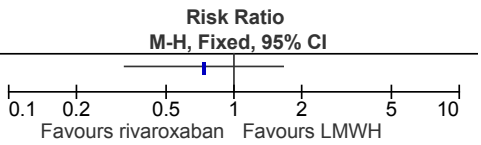
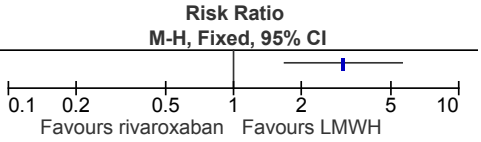


Figure 130: Major bleeding (35 days)

Study or Subgroup	Rivaroxaban Events	Total	LMWH Events	Total	Risk Ratio M-H, Fixed, 95% CI
Cohen 2013	43	3997	14	4001	3.07 [1.68, 5.61]



L.13.11 Fondaparinux versus no prophylaxis

Figure 131: All-cause mortality (30 days)

Study or Subgroup	Fondaparinux Events	Total	No prophylaxis Events	Total	Risk Ratio M-H, Fixed, 95% CI
Cohen 2006	14	425	25	414	0.55 [0.29, 1.03]

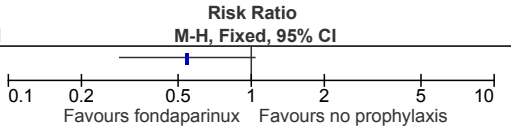


Figure 132: DVT (symptomatic and asymptomatic) (15 days)

Study or Subgroup	Fondaparinux Events	Total	No prophylaxis Events	Total	Risk Ratio M-H, Fixed, 95% CI
Cohen 2006	18	321	29	323	0.62 [0.35, 1.10]

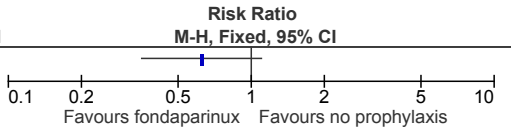


Figure 133: PE (30 days)

Study or Subgroup	Fondaparinux Events	Total	No prophylaxis Events	Total	Risk Ratio M-H, Fixed, 95% CI
Cohen 2006	1	425	4	414	0.24 [0.03, 2.17]

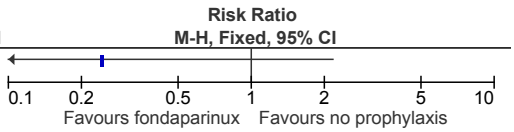


Figure 134: Major bleeding (15 days)

Study or Subgroup	Fondaparinux Events	Total	No prophylaxis Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Cohen 2006	1	425	1	414	0.97 [0.06, 15.60]

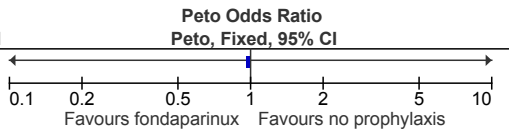
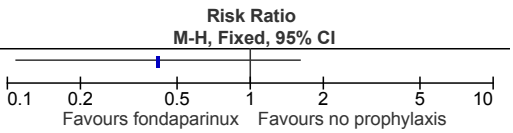


Figure 135: Fatal PE (30 days)

Study or Subgroup	Fondaparinux Events	Total	No prophylaxis Events	Total	Risk Ratio M-H, Fixed, 95% CI
Cohen 2006	3	425	7	414	0.42 [0.11, 1.60]



L.14 Cancer

L.14.1 LMWH (standard dose) versus no prophylaxis

Figure 136: All-cause mortality

Study or Subgroup	LMWH Events	Total	No prophylaxis Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haas 2012 - TOPIC 1	15	174	12	178	14.3%	1.28 [0.62, 2.65]
Haas 2012 - TOPIC 2	55	273	59	273	71.2%	0.93 [0.67, 1.29]
Perry 2010	18	91	11	76	14.5%	1.37 [0.69, 2.71]
Total (95% CI)		**538**		**527**	**100.0%**	**1.04 [0.80, 1.37]**
Total events	88		82			

Heterogeneity: Chi² = 1.35, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)

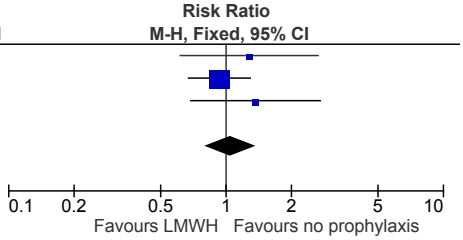


Figure 137: DVT (symptomatic & asymptomatic)

Study or Subgroup	LMWH Events	Total	No prophylaxis Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haas 2012 - TOPIC 1	4	174	5	177	15.5%	0.81 [0.22, 2.98]
Haas 2012 - TOPIC 2	8	268	16	264	50.4%	0.49 [0.21, 1.13]
Perry 2010	8	91	10	76	34.1%	0.67 [0.28, 1.61]
Total (95% CI)		**533**		**517**	**100.0%**	**0.60 [0.35, 1.04]**
Total events	20		31			

Heterogeneity: Chi² = 0.48, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.82 (P = 0.07)

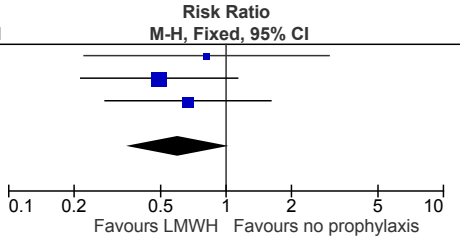


Figure 138: Pulmonary embolism

Study or Subgroup	LMWH Events	Total	No prophylaxis Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haas 2012 - TOPIC 1	1	174	1	177	7.6%	1.02 [0.06, 16.14]
Haas 2012 - TOPIC 2	2	268	4	264	31.1%	0.49 [0.09, 2.67]
Pelzer 2015	0	160	3	152	27.7%	0.14 [0.01, 2.61]
Perry 2010	2	91	4	76	33.6%	0.42 [0.08, 2.22]
Total (95% CI)		**693**		**669**	**100.0%**	**0.41 [0.15, 1.10]**
Total events	5		12			

Heterogeneity: Chi² = 1.00, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)

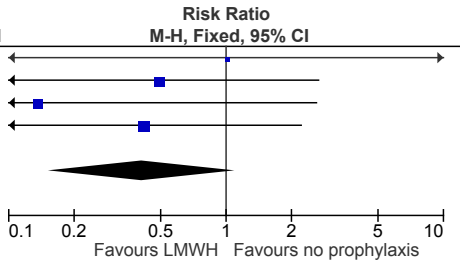


Figure 139: Major bleeding

Study or Subgroup	LMWH Events	Total	No prophylaxis Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haas 2012 - TOPIC 1	3	174	0	178	4.1%	7.16 [0.37, 137.60]
Haas 2012 - TOPIC 2	10	273	6	273	49.3%	1.67 [0.61, 4.52]
Pelzer 2015	7	160	5	152	42.1%	1.33 [0.43, 4.10]
Perry 2010	3	91	0	76	4.5%	5.86 [0.31, 111.68]
Total (95% CI)		**698**		**679**	**100.0%**	**1.94 [0.98, 3.84]**
Total events	23		11			

Heterogeneity: Chi² = 1.81, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)

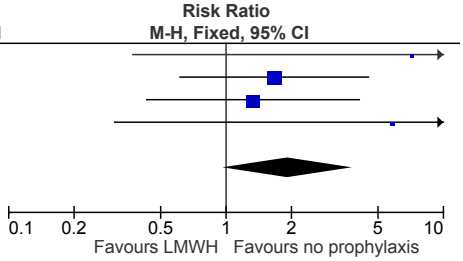
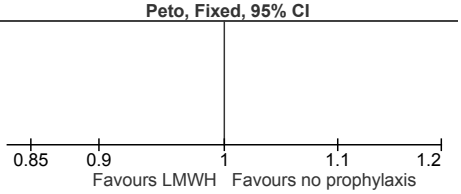


Figure 140: Heparin-induced thrombocytopenia

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Haas 2012 - TOPIC 1	0	174	0	178		Not estimable
Haas 2012 - TOPIC 2	0	273	0	273		Not estimable
Total (95% CI)		**447**		**451**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



L.14.2 LMWH (high-dose) versus no prophylaxis

Figure 141: All-cause mortality

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Agnelli 2009	33	769	16	381	1.02 [0.57, 1.83]

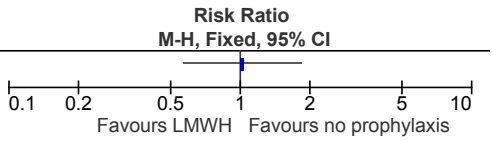


Figure 142: DVT (symptomatic & asymptomatic)

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Agnelli 2009	14	496	12	270	0.64 [0.30, 1.35]

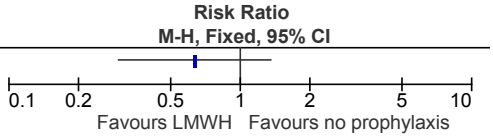


Figure 143: Pulmonary embolism

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Agnelli 2009	3	496	3	270	0.54 [0.11, 2.68]

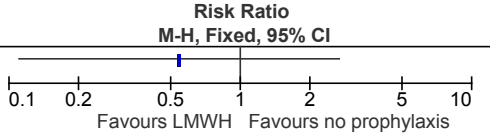
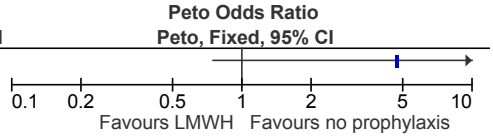


Figure 144: Major bleeding

Study or Subgroup	LMWH Events	LMWH Total	No prophylaxis Events	No prophylaxis Total	Peto Odds Ratio Peto, Fixed, 95% CI
Agnelli 2009	5	496	0	270	4.72 [0.75, 29.73]



L.14.3 LMWH (standard dose) verus aspirin

Figure 145: All-cause mortality

Study or Subgroup	LMWH Events	LMWH Total	Aspirin Events	Aspirin Total	Peto Odds Ratio Peto, Fixed, 95% CI
Larocca 2012	0	166	0	176	Not estimable
Palumbo 2011	1	219	1	220	1.00 [0.06, 16.11]

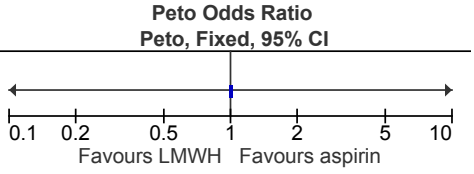


Figure 146: Pulmonary embolism

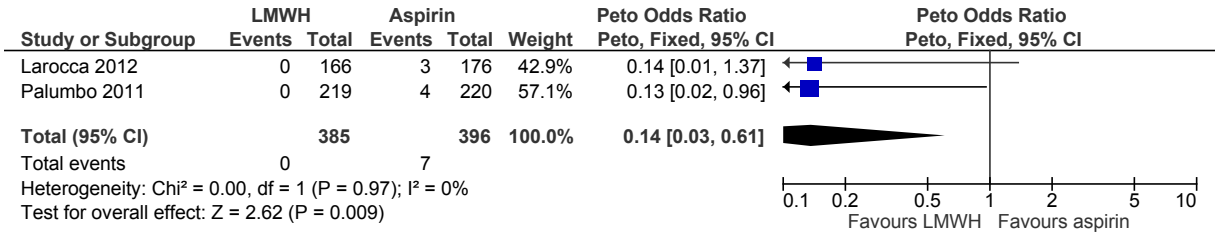
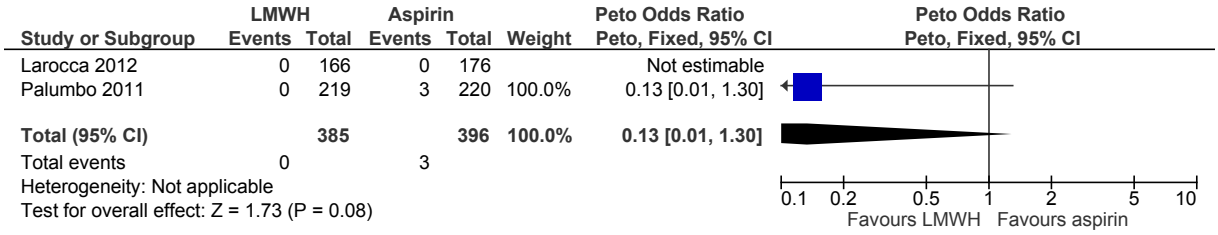


Figure 147: Major bleeding



L.14.4 Apixaban versus no prophylaxis

Figure 148: All-cause mortality

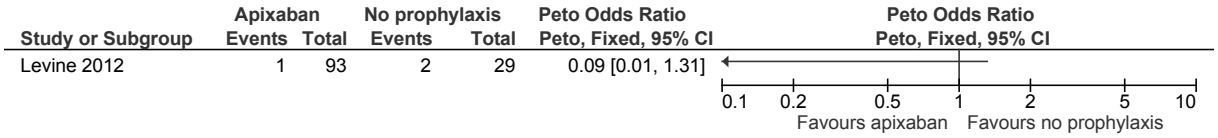


Figure 149: Pulmonary embolism

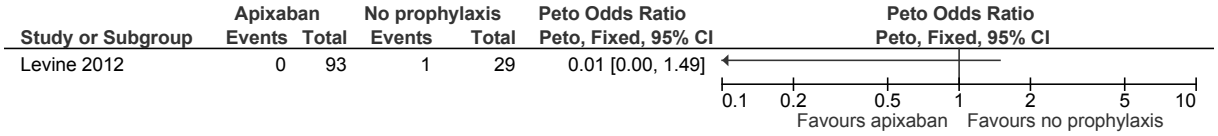


Figure 150: Major bleeding

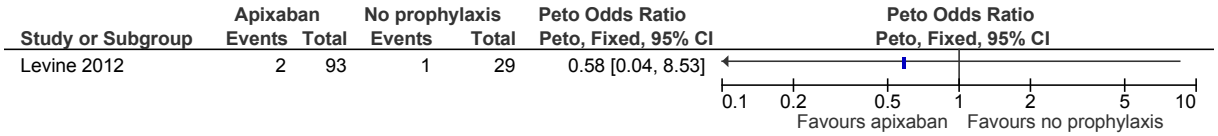
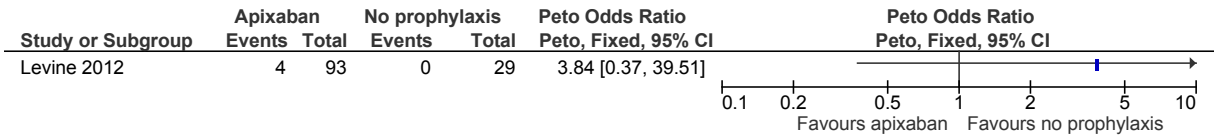


Figure 151: Clinically relevant non-major bleeding



L.14.5 VKA versus no prophylaxis

Figure 152: All-cause mortality

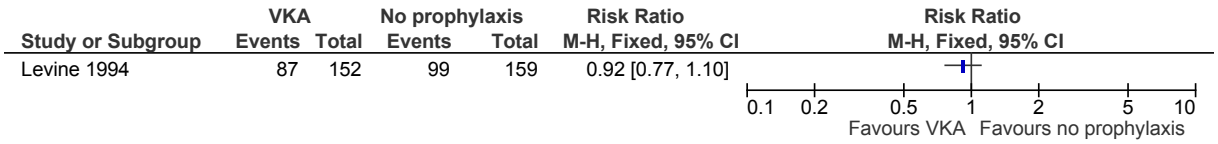


Figure 153: Pulmonary embolism

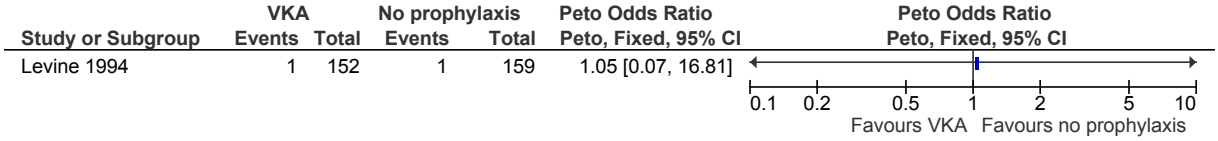
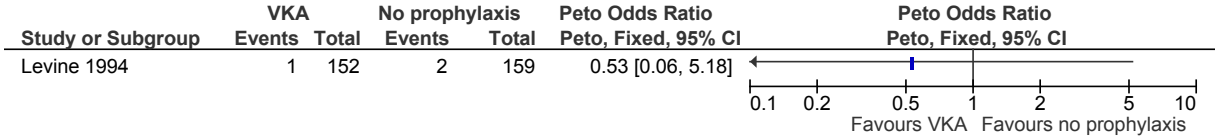


Figure 154: Major bleeding



L.15 Patients with central venous catheters

L.15.1 LMWH (standard dose; standard duration) versus no VTE prophylaxis

Figure 155: All-cause mortality (30–112 days)

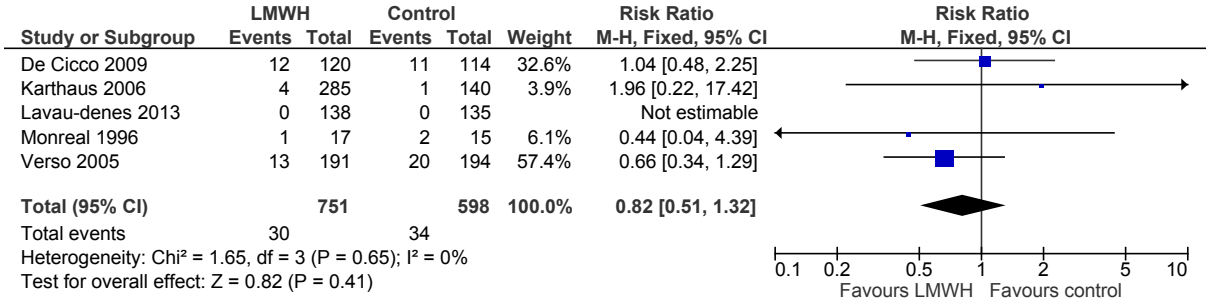


Figure 156: DVT (30–90 days)

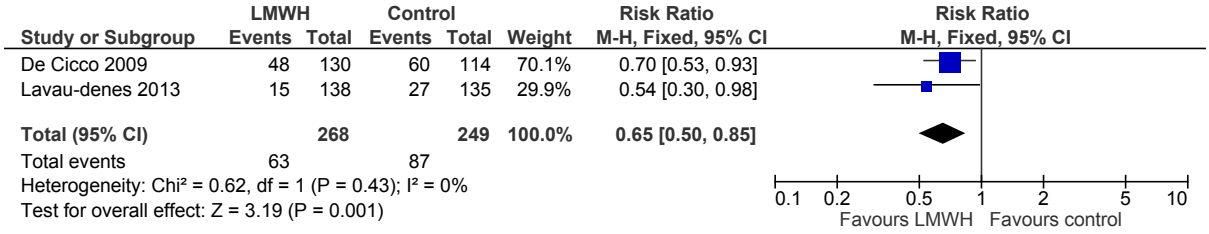


Figure 157: PE (90–112 days)

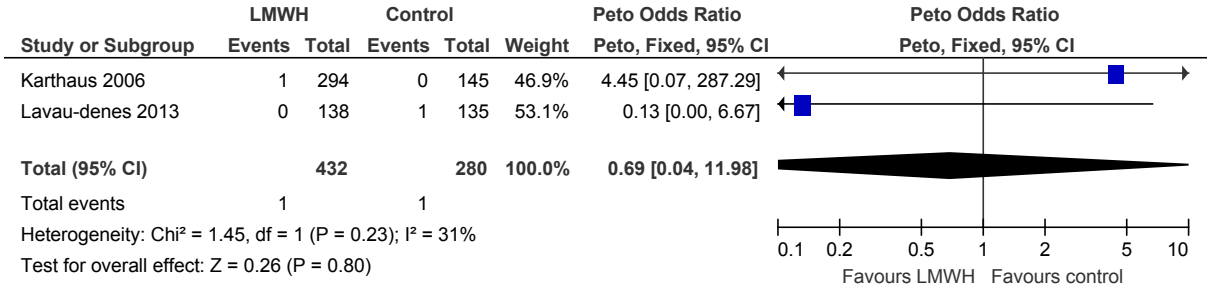


Figure 158: PE, fatal (90 days)

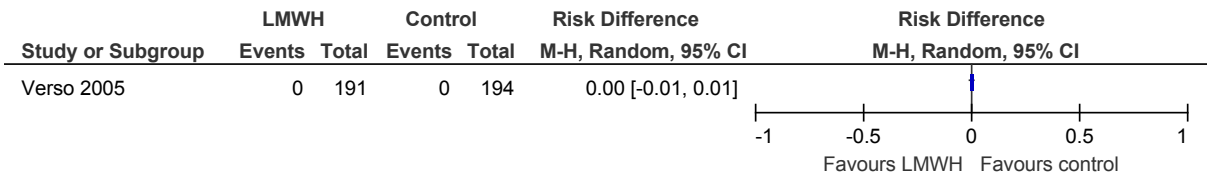
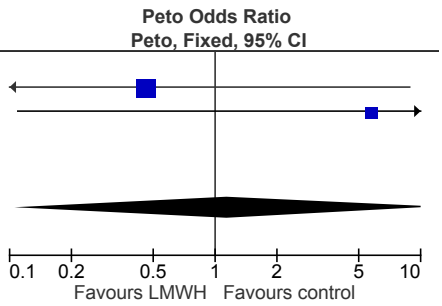


Figure 159: Major bleeding (30–112 days)

Study or Subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
De Cicco 2009	0	114	0	114		Not estimable
Karthaus 2006	1	294	1	145	64.3%	0.46 [0.02, 8.86]
Monreal 1996	1	16	0	12	35.7%	5.75 [0.11, 302.04]
Niers 2007	0	56	0	57		Not estimable
Verso 2005	0	191	0	194		Not estimable
Total (95% CI)		**671**		**522**	**100.0%**	**1.14 [0.11, 12.13]**
Total events	2		1			

Heterogeneity: Chi² = 1.00, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)



L.15.2 LMWH (low dose; standard duration) versus no VTE prophylaxis

Figure 160: Major bleeding (21 days)

Study or Subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Risk Difference M-H, Fixed, 95% CI
Niers 2007	0	56	0	57	0.00 [-0.03, 0.03]

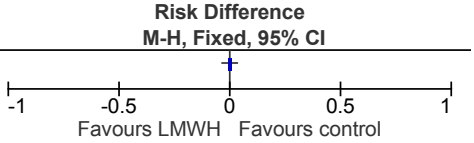


Figure 161: Clinically relevant non-major bleeding

Study or Subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Risk Difference M-H, Fixed, 95% CI
Niers 2007	0	56	0	57	0.00 [-0.03, 0.03]

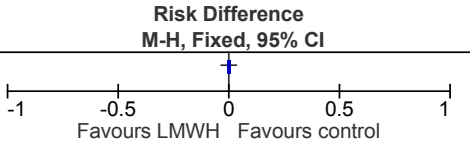
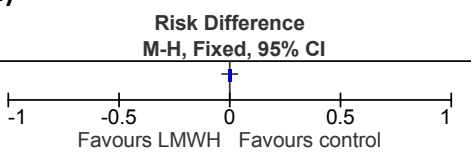


Figure 162: Heparin-induced thrombocytopenia (21 days)

Study or Subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Risk Difference M-H, Fixed, 95% CI
Niers 2007	0	56	0	57	0.00 [-0.03, 0.03]



L.15.3 VKA versus no VTE prophylaxis

Figure 163: All-cause mortality (30 days)

Study or Subgroup	VKA Events	VKA Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
De Cicco 2009	14	114	11	114	1.27 [0.60, 2.68]

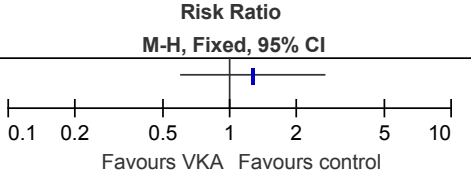
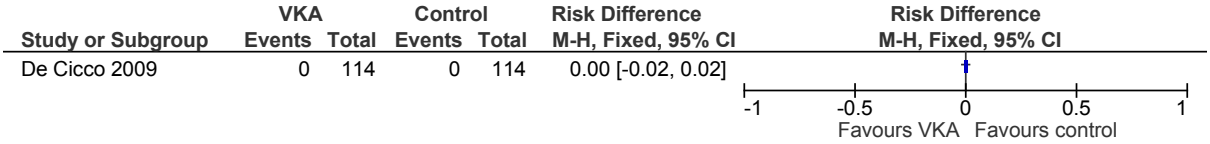


Figure 164: DVT (30 days)

Figure 165: Major bleeding (30 days)



L.15.4 LMWH (standard dose; standard duration) versus VKA

Figure 166: All-cause mortality (30 days)

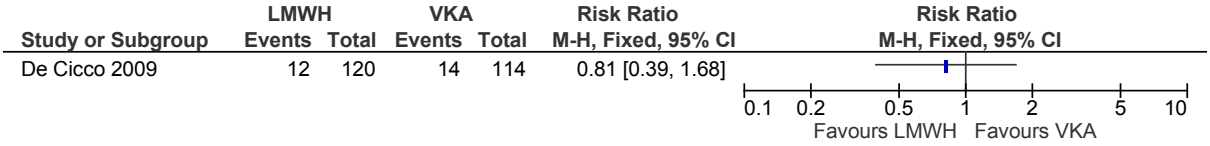


Figure 167: DVT (30 days)

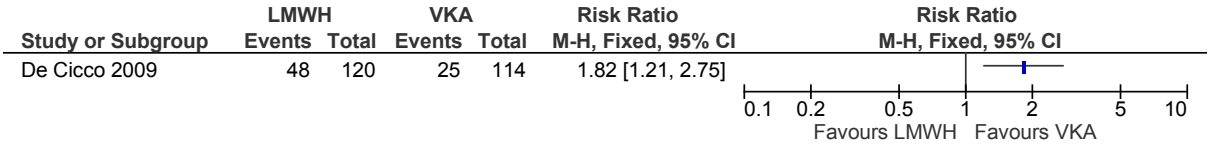
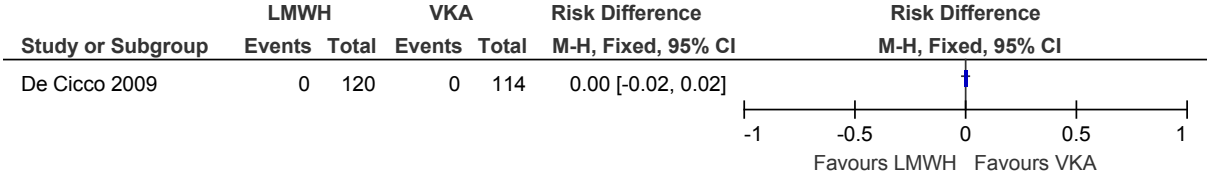


Figure 168: Major bleeding (30 days)



L.16 Palliative care

No relevant clinical studies identified.

L.17 Critical care

L.17.1 People who are not contraindicated to pharmacological or mechanical prophylaxis

L.17.1.1 LMWH (standard dose; standard duration) versus UFH

Figure 169: Mortality in ICU and hospital (up to 100 days)

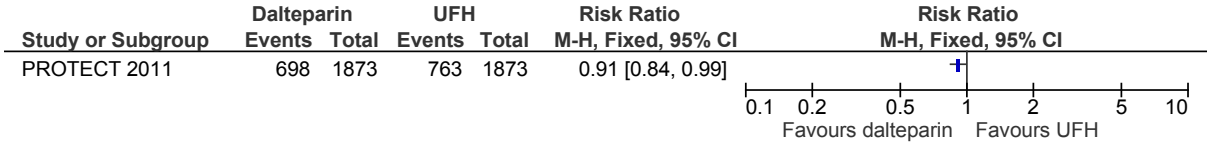


Figure 170: DVT (symptomatic or asymptomatic) (Time of death, discharge or at 100 days if patients were still hospitalised)

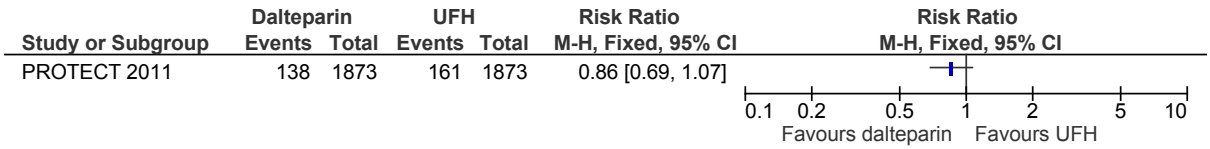


Figure 171: PE (Time of death, discharge or at 100 days if patients were still hospitalised)

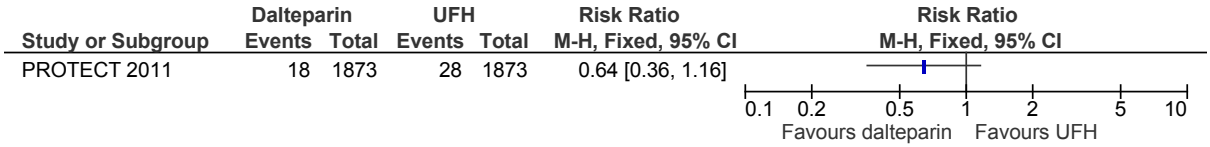


Figure 172: Major bleeding (Time of death, discharge or at 100 days if patients were still hospitalised)

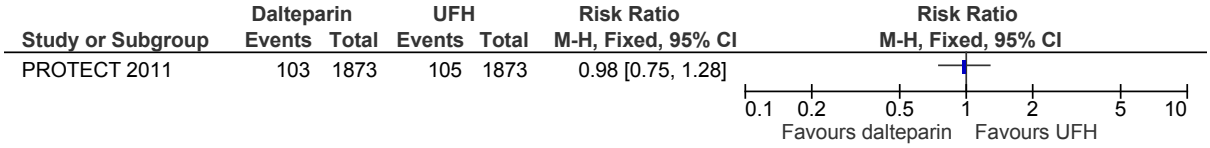
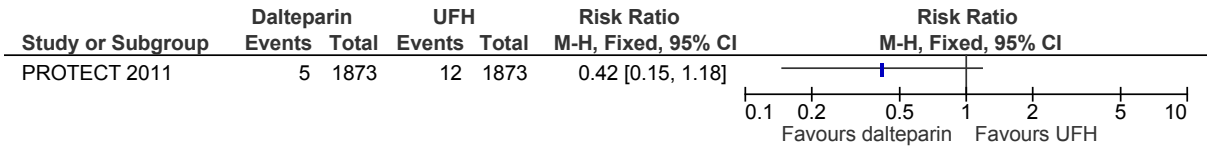


Figure 173: Heparin-induced thrombocytopenia (Time of death, discharge or at 100 days if patients were still hospitalised)



L.17.2 People contraindicated to pharmacological prophylaxis

L.17.2.1 IPC (half-leg) and AES versus AES

Figure 174: DVT (symptomatic and symptomatic) (6 days)

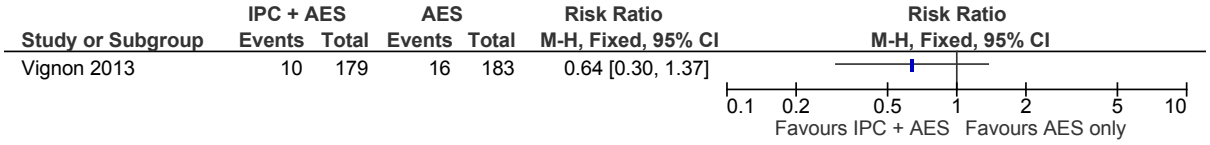


Figure 175: PE (6 days)

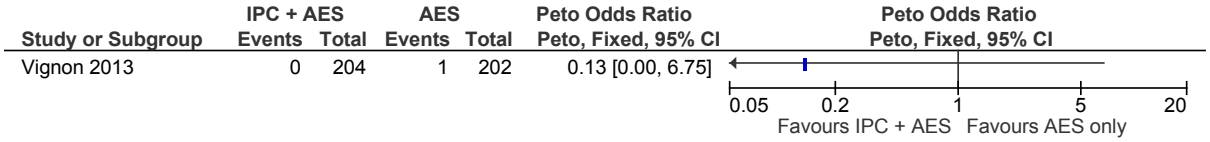
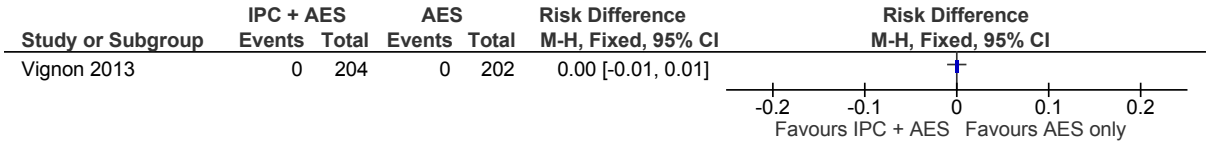


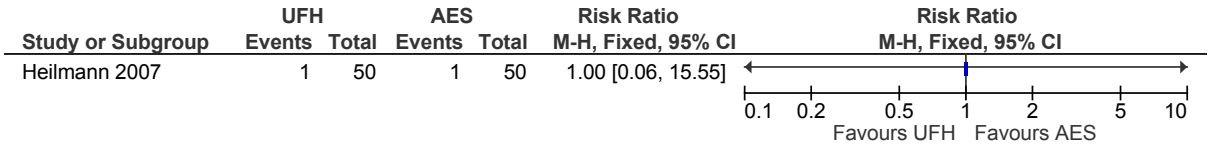
Figure 176: Fatal PE (6 days)



L.18 Pregnant women and women up to 6 weeks postpartum

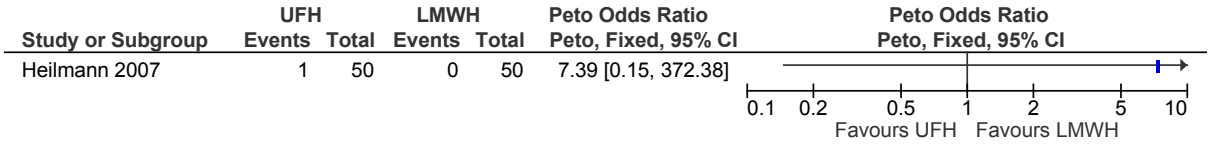
L.18.1 UFH versus AES (length unspecified)

Figure 177: DVT (symptomatic and asymptomatic) (at discharge, duration of hospital stay not reported)



L.18.2 UFH versus LMWH (standard dose; standard duration)

Figure 178: DVT (symptomatic and asymptomatic) (at discharge, duration of hospital stay not reported)



L.18.3 LMWH (low dose; standard duration) versus no prophylaxis

Figure 179: PE (42 days)

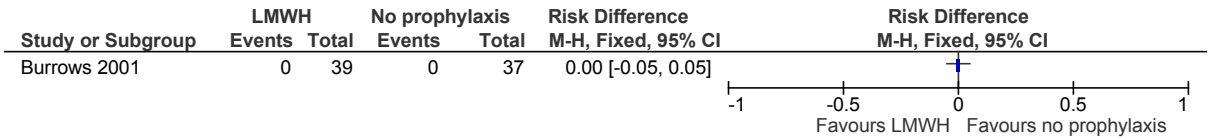
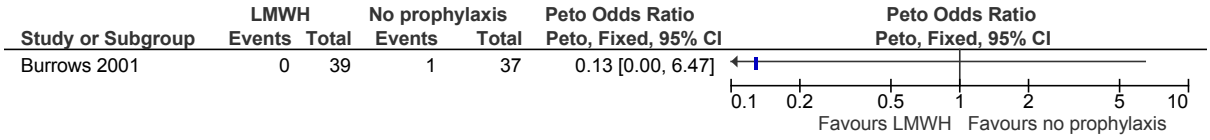
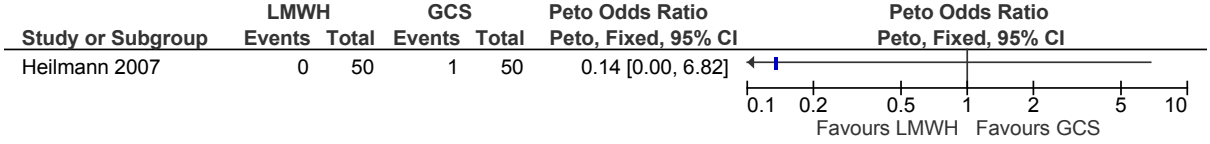


Figure 180: Major bleeding (42 days)



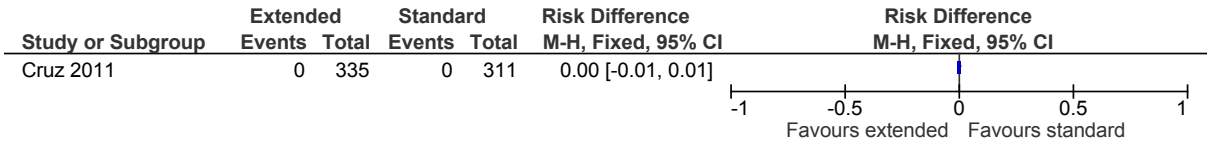
L.18.4 LMWH (standard dose, standard duration) versus AES (length unspecified)

Figure 181: DVT (at discharge, duration of hospital stay not reported)



L.18.5 LMWH (high dose, extended duration) versus LMWH (high dose, standard duration)

Figure 182: PE (90 days)



L.19 People with psychiatric illness

No relevant clinical studies identified.

L.20 Anaesthesia

L.20.1 Regional vs General Anaesthesia

Figure 183: Regional vs General Anaesthesia - DVT

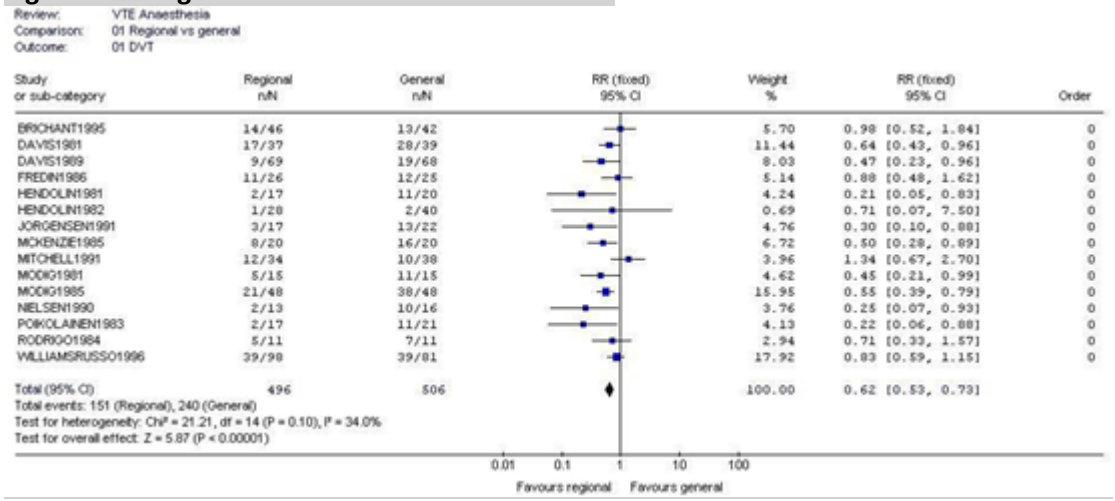


Figure 184: Regional vs General Anaesthesia – Pulmonary Embolism

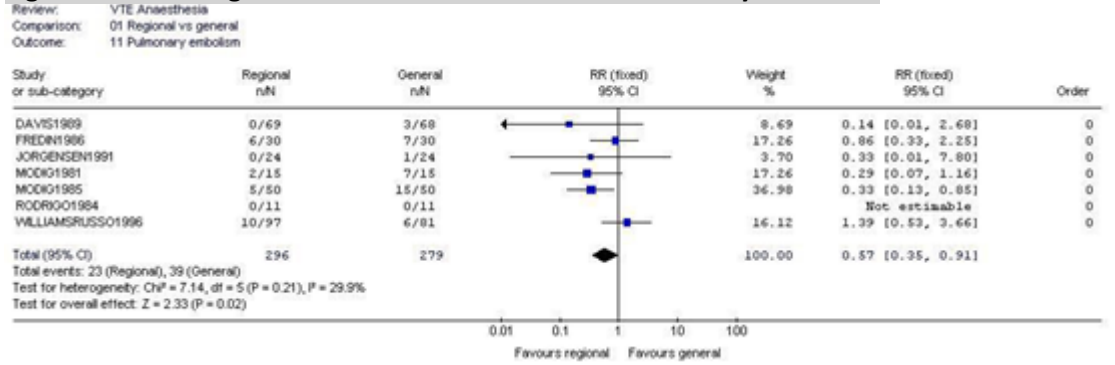


Figure 185: Regional vs General Anaesthesia – Proximal DVT

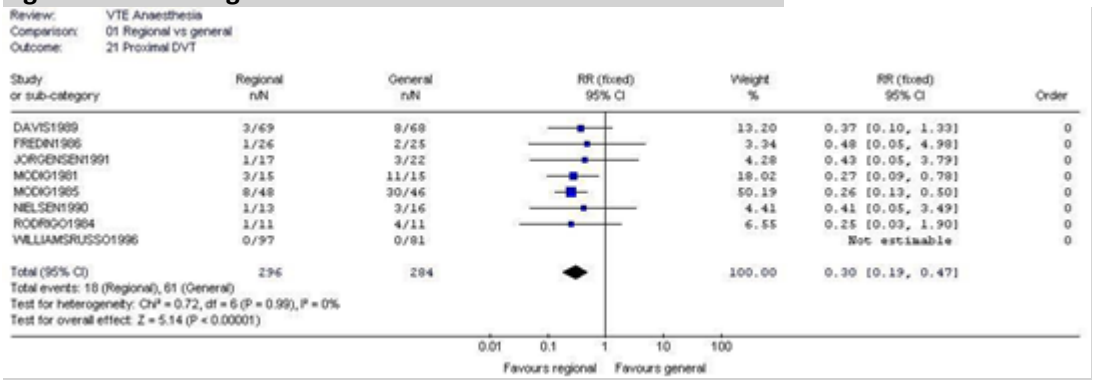
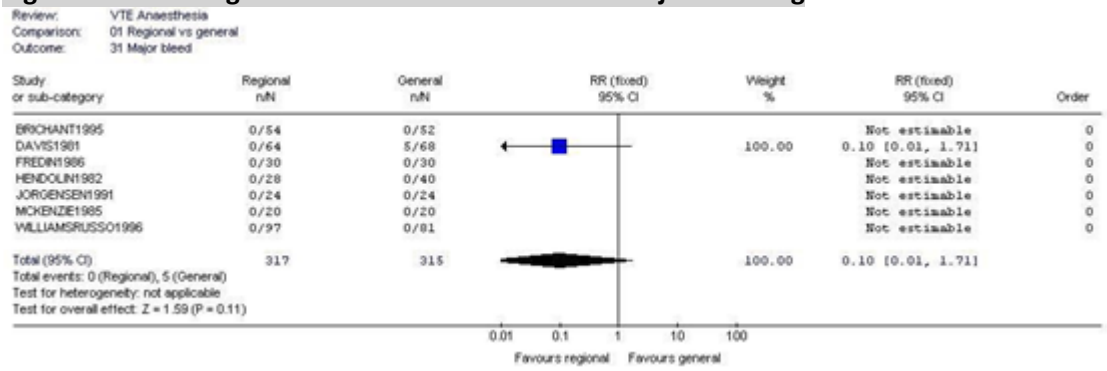


Figure 186: Regional vs General Anaesthesia – Major Bleeding



L.20.2 Regional vs General Anaesthesia Subgrouped by Spinal and Epidural

Figure 187: Regional vs General Anaesthesia Subgrouped by Spinal and Epidural - DVT

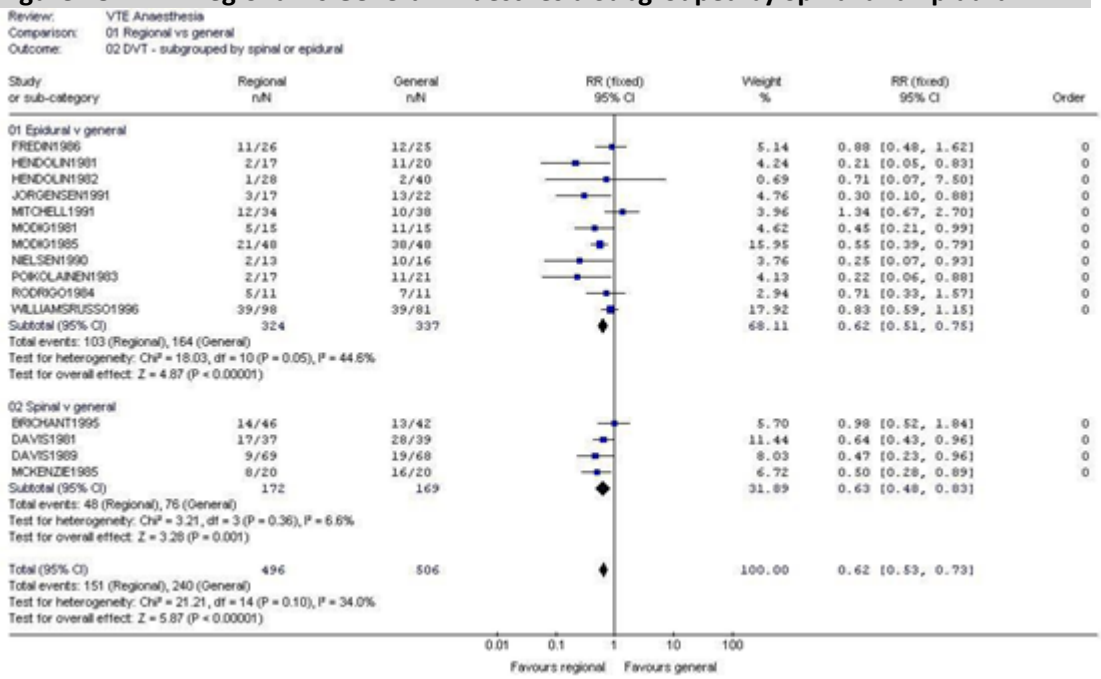
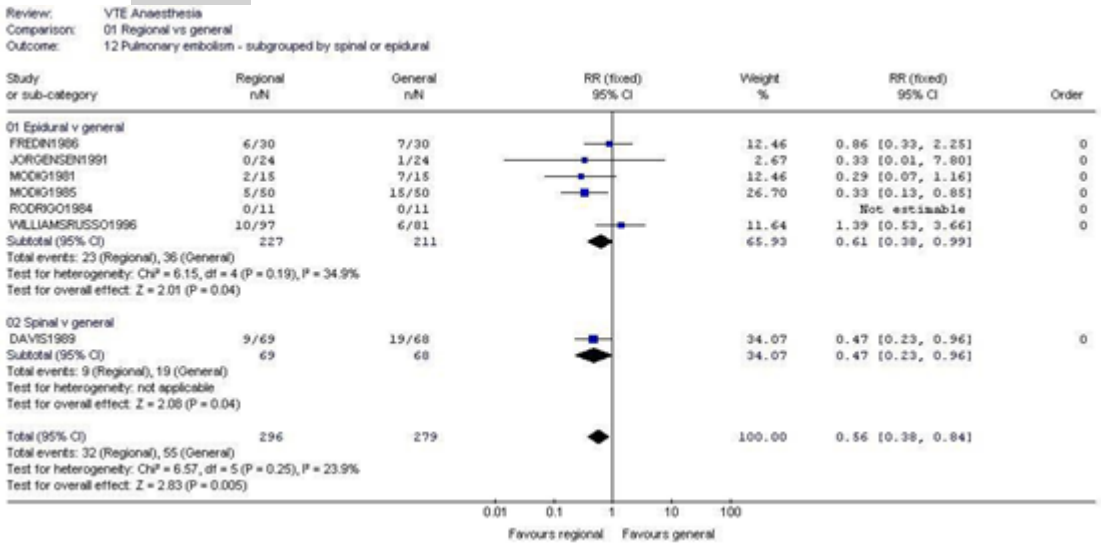
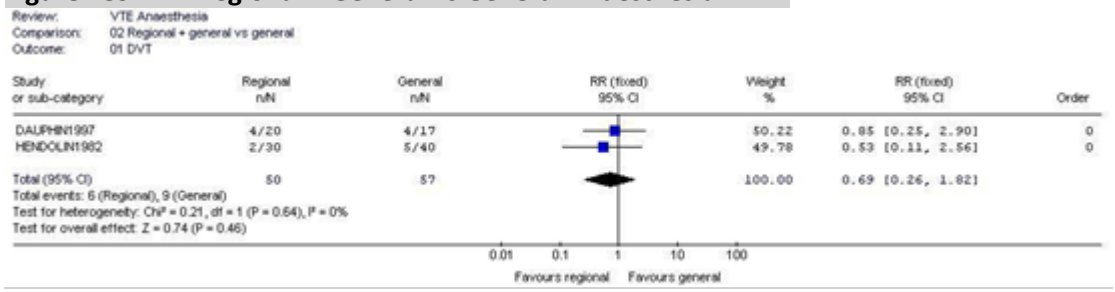


Figure 188: Regional vs General Anaesthesia Subgrouped by Spinal and Epidural – Pulmonary Embolism



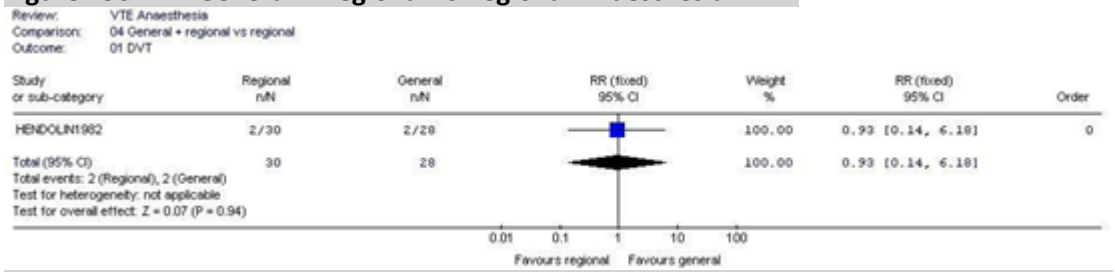
L.20.3 Regional + General vs General Anaesthesia

Figure 189: Regional + General vs General Anaesthesia - DVT



L.20.4 General + Regional vs Regional Anaesthesia

Figure 190: General + Regional vs Regional Anaesthesia - DVT



L.21 Lower limb immobilisation

L.21.1 IPCD (below knee) versus no VTE prophylaxis

Figure 191: PE (42 days)

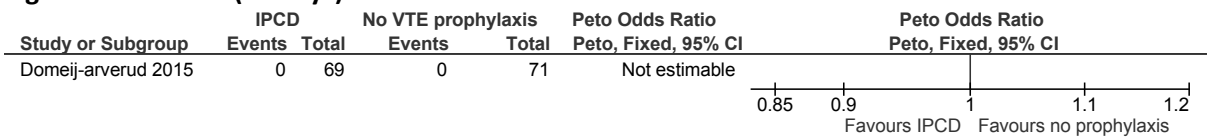


Figure 192: DVT (42 days)

L.21.2 LMWH (standard prophylactic dose) versus no VTE prophylaxis

Figure 193: All-cause mortality (42 days)

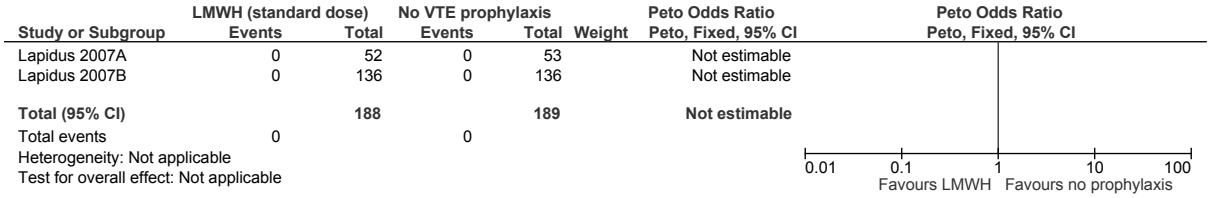


Figure 194: Fatal PE (38-42 days)

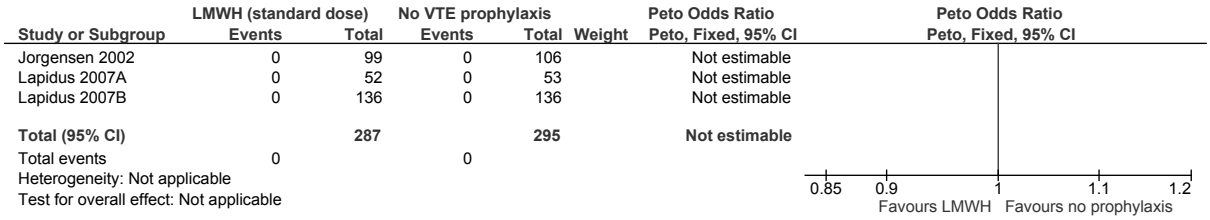


Figure 195: PE (38 days until plaster cast removed)

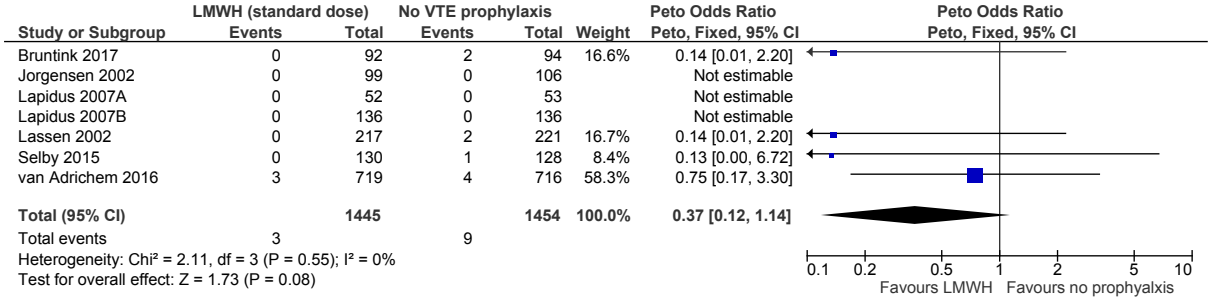


Figure 196: DVT (38 days until plaster cast removed)

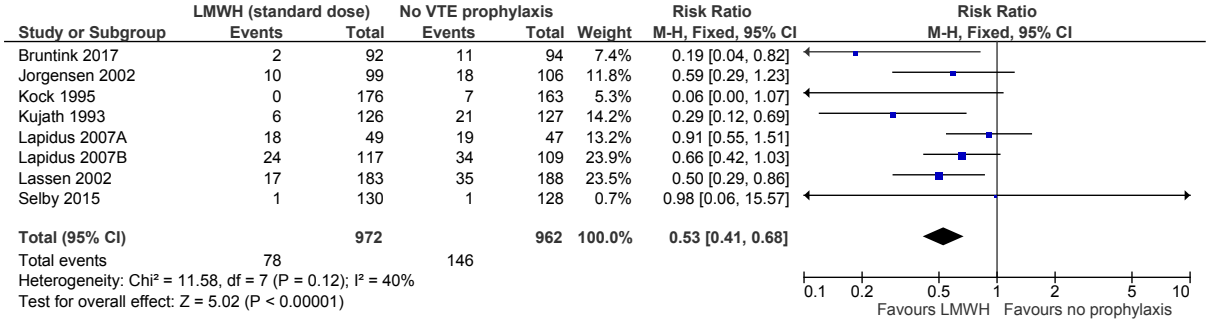


Figure 197: Major bleeding (42-90 days)

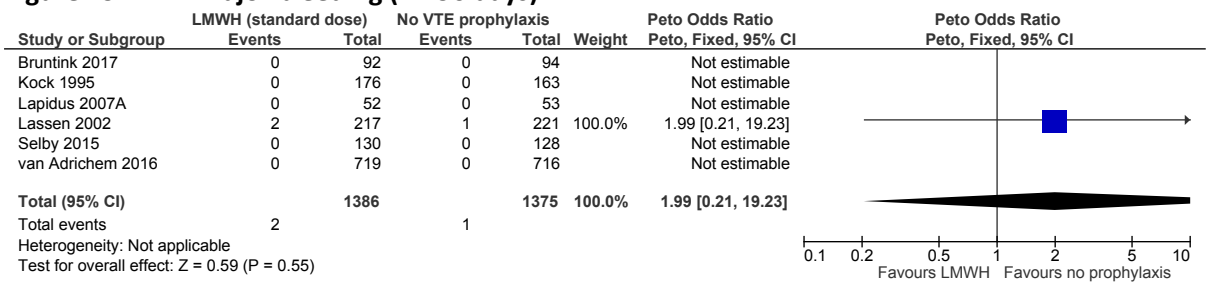


Figure 198: Clinically relevant non-major bleeding (5 weeks)

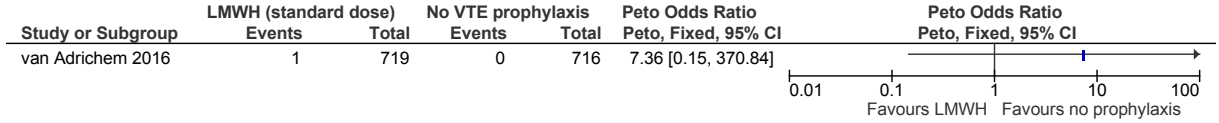
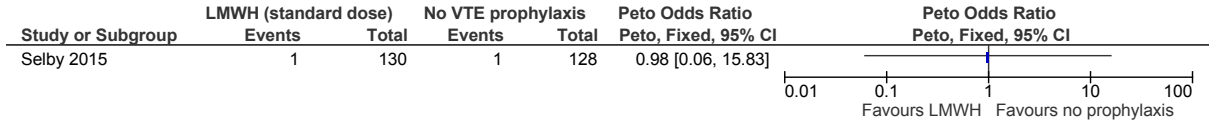


Figure 199: Heparin-induced thrombocytopenia (90 days)



L.21.3 Foundaparinux versus no VTE prophylaxis

Figure 200: PE

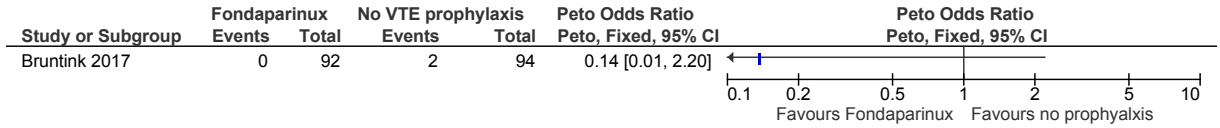


Figure 201: DVT

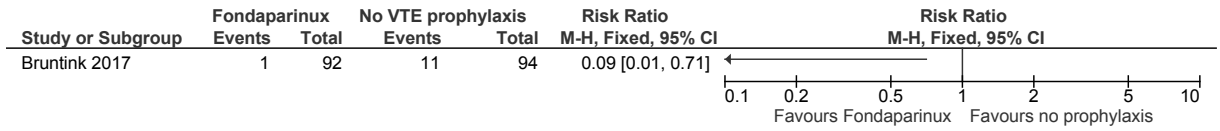
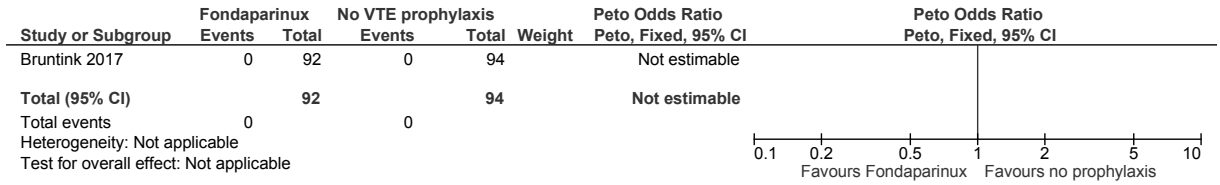


Figure 202: Major bleeding



L.21.4 Fondaparinux versus LMWH (standard prophylactic dose)

Figure 203: All-cause mortality (21-45 days)

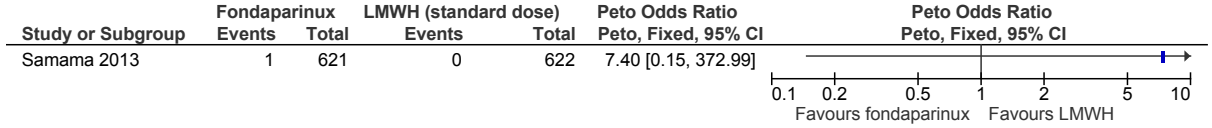


Figure 204: PE (21-45 days)

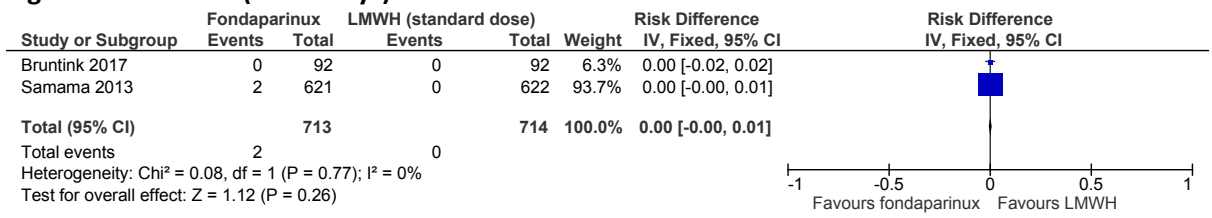


Figure 205: DVT (21-45 days)

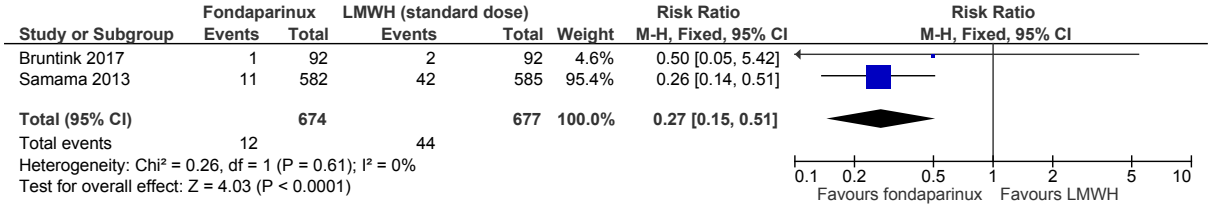


Figure 206: Major bleeding (21-45 days)

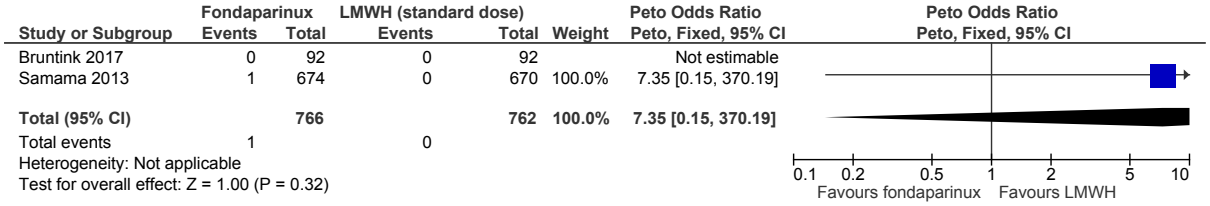


Figure 207: Clinically relevant non-major bleeding (21-45 days)

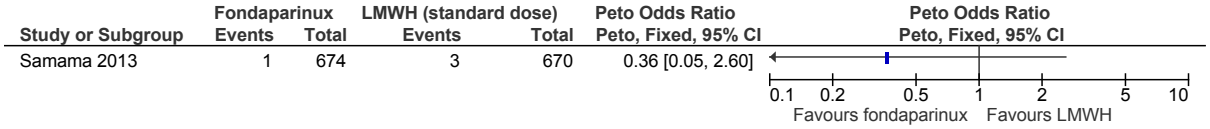
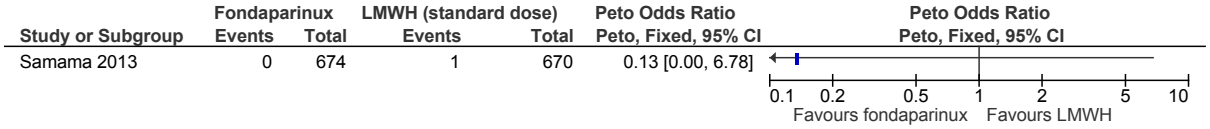


Figure 208: Heparin-induced thrombocytopenia (21-45 days)



L.22 Fragility fractures of the pelvis, hip and proximal femur

L.22.1 LMWH (standard dose; standard duration) versus no prophylaxis

Figure 209: All-cause mortality (84 days)

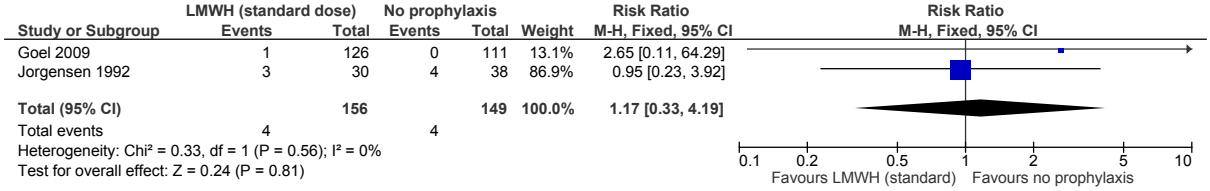


Figure 210: DVT (symptomatic and asymptomatic) (9 days)

Study or Subgroup	LMWH (standard dose) Events	Total	No prophylaxis Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goel 2009	11	126	14	111	43.4%	0.69 [0.33, 1.46]
Jorgensen 1992	9	30	22	38	56.6%	0.52 [0.28, 0.95]
Total (95% CI)		**156**		**149**	**100.0%**	**0.59 [0.37, 0.96]**
Total events	20		36			

Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)

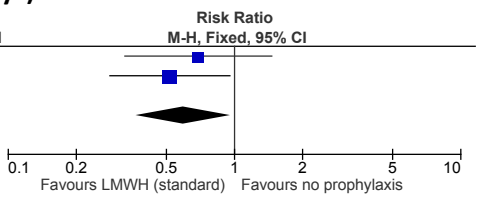


Figure 211: PE (84 days)

Study or Subgroup	LMWH (standard dose) Events	Total	No prophylaxis Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Jorgensen 1992	0	30	1	38	0.17 [0.00, 8.65]

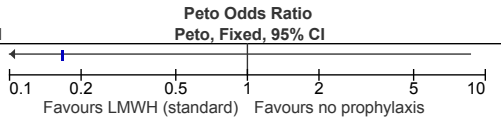


Figure 212: Wound infection (84 days)

Study or Subgroup	LMWH (standard dose) Events	Total	No prophylaxis Events	Total	Risk Ratio M-H, Fixed, 95% CI
Jorgensen 1992	2	30	2	38	1.27 [0.19, 8.47]

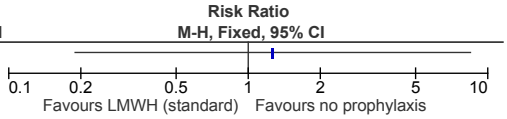
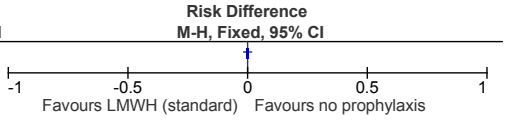


Figure 213: Major bleeding (time-point not reported)

Study or Subgroup	LMWH (standard dose) Events	Total	No prophylaxis Events	Total	Risk Difference M-H, Fixed, 95% CI
Goel 2009	0	126	0	111	0.00 [-0.02, 0.02]



L.22.2 LMWH (standard dose; standard duration) versus UFH

Figure 214: All-cause mortality (time-point not reported)

Study or Subgroup	LMWH (standard dose) Events	Total	UFH Events	Total	Risk Ratio M-H, Fixed, 95% CI
Monreal 1989A	2	46	3	44	0.64 [0.11, 3.64]

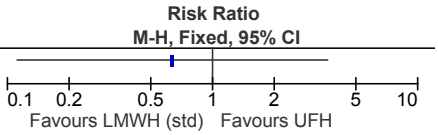
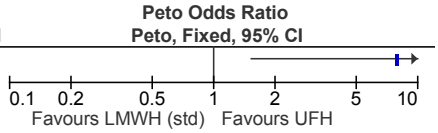


Figure 215: PE (8 days)

Study or Subgroup	LMWH (standard dose) Events	Total	UFH Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Monreal 1989A	6	46	0	44	7.95 [1.53, 41.29]



L.22.3 LMWH (standard dose; standard duration) versus fondaparinux

Figure 216: All-cause mortality (49 days)

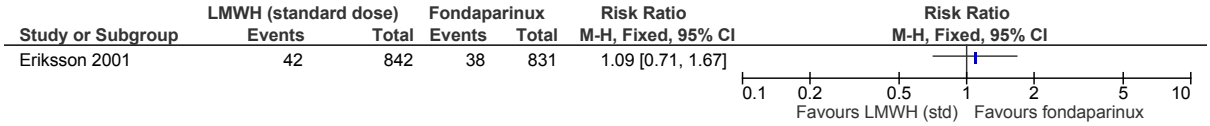


Figure 217: DVT (symptomatic and asymptomatic) (11 days)

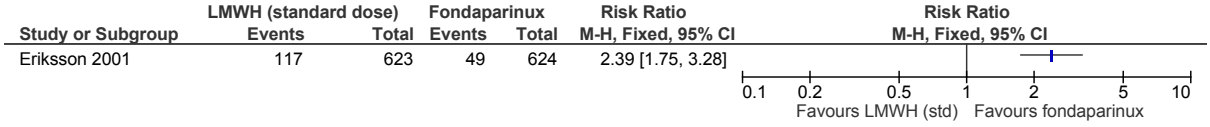


Figure 218: PE (11 days)

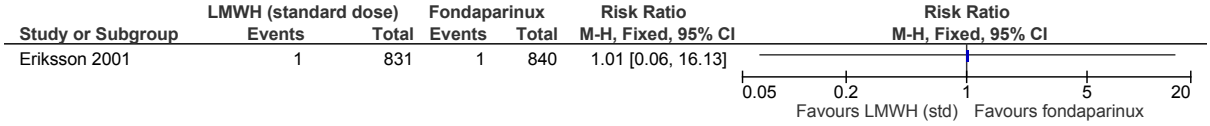


Figure 219: Major bleeding (11 days)

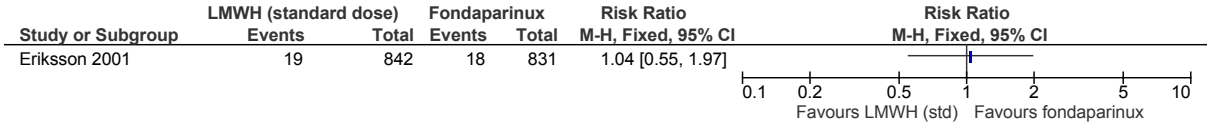
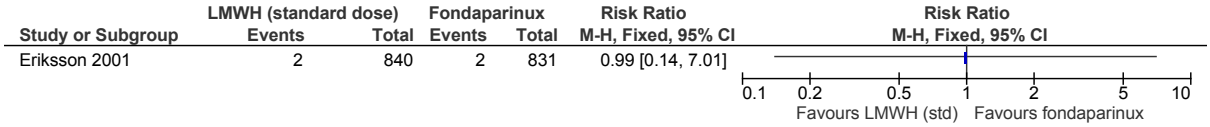


Figure 220: Fatal PE (11 days)



L.22.4 LMWH (standard dose; standard duration) followed by rivaroxaban versus rivaroxaban

Figure 221: All-cause mortality (30 days)

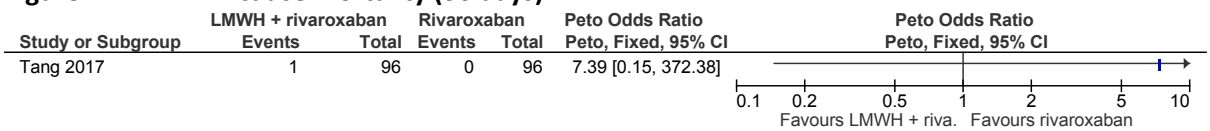


Figure 222: DVT (symptomatic and asymptomatic) (30 days)

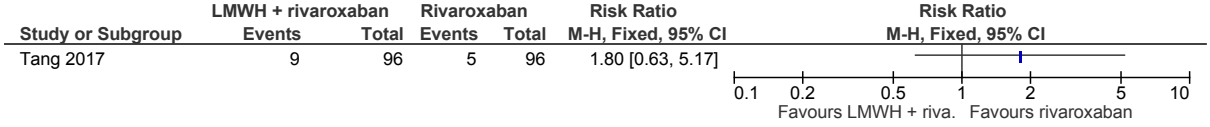


Figure 223: PE (30 days)

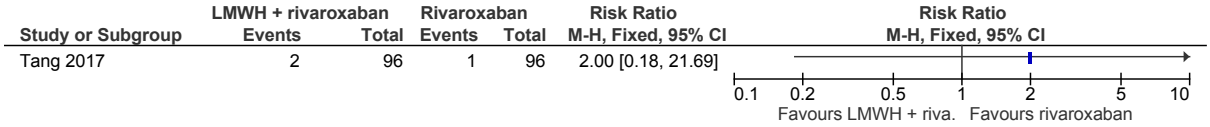
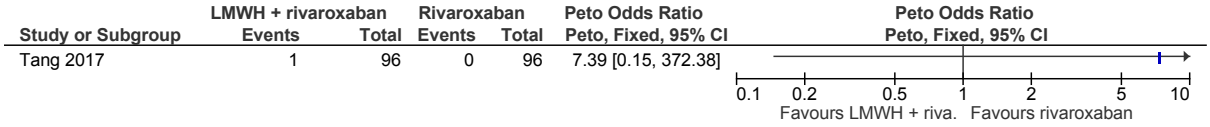


Figure 224: Fatal PE (30 days)



L.22.5 LMWH (standard dose; standard duration) followed by rivaroxaban versus LMWH (standard dose; extended duration)

Figure 225: All-cause mortality (30 days)

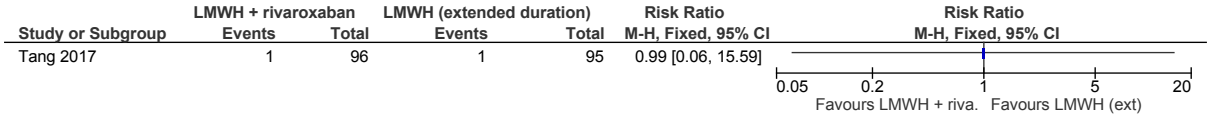


Figure 226: DVT (symptomatic and asymptomatic) (30 days)

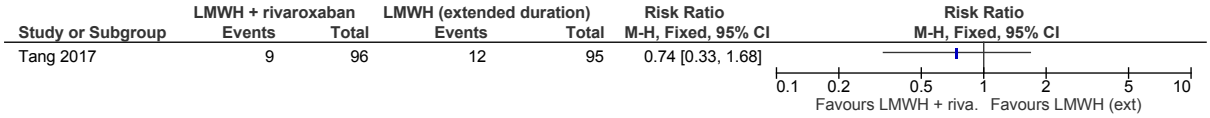


Figure 227: PE (30 days)

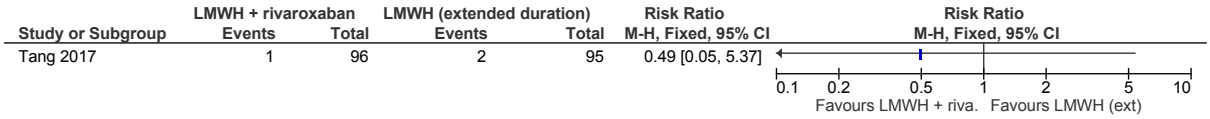
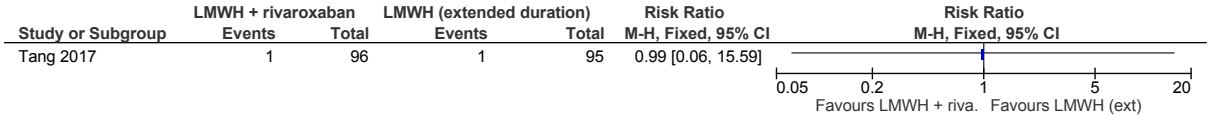


Figure 228: Fatal PE (30 days)



L.22.6 LMWH (standard dose; extended duration) versus rivaroxaban

Figure 229: All-cause mortality (30 days)

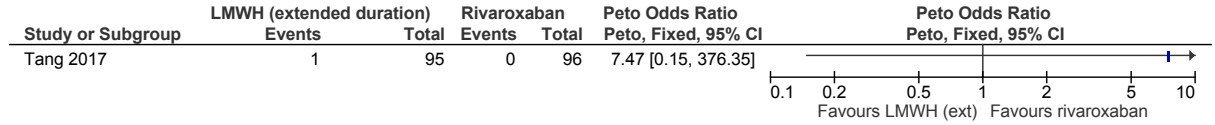


Figure 230: DVT (symptomatic and asymptomatic) (30 days)

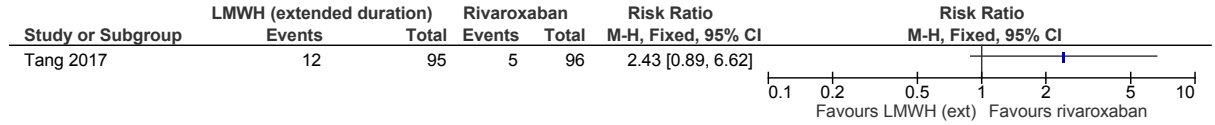


Figure 231: PE (30 days)

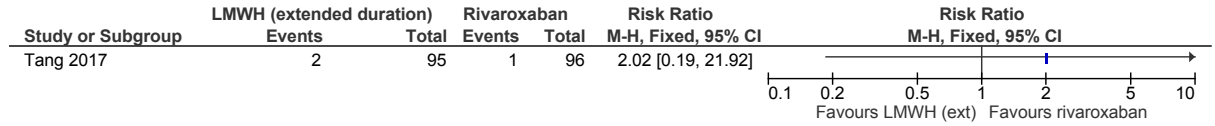
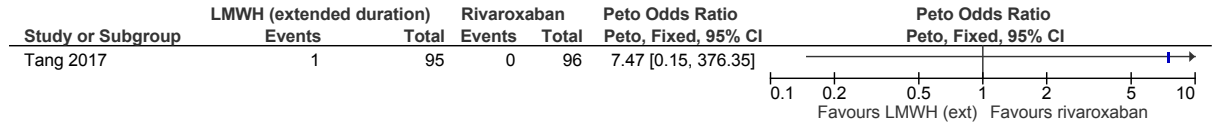


Figure 232: Fatal PE (30 days)



L.22.7 Fondaparinux (extended duration) versus fondaparinux (standard duration)

Figure 233: All-cause mortality (25-31 days)

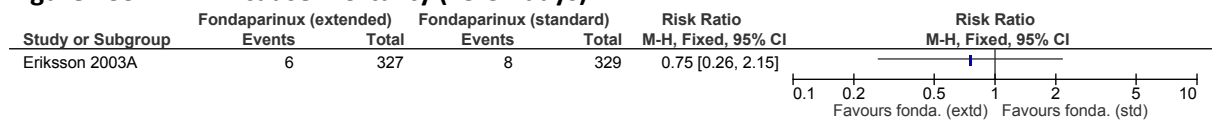


Figure 234: DVT (symptomatic and asymptomatic) (25-32 days)

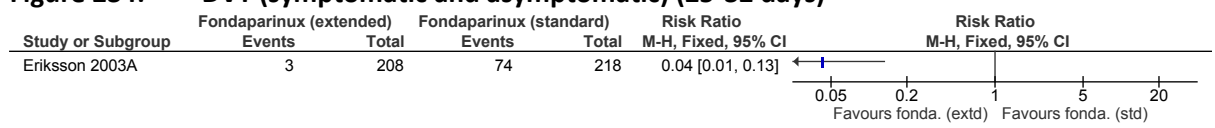


Figure 235: PE (25-31 days)

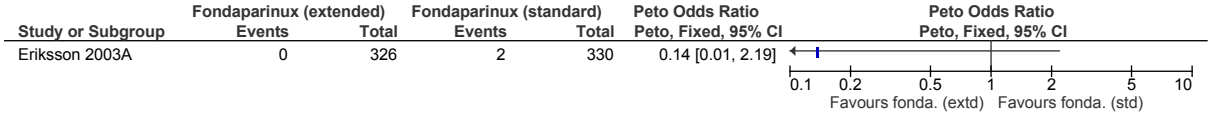


Figure 236: Major bleeding (25-31 days)

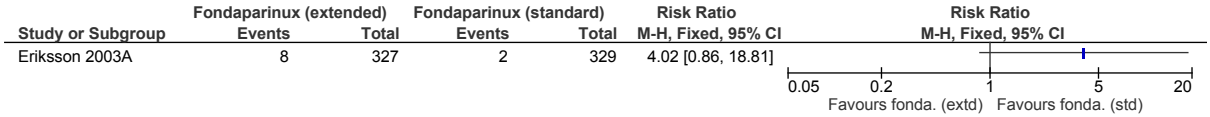
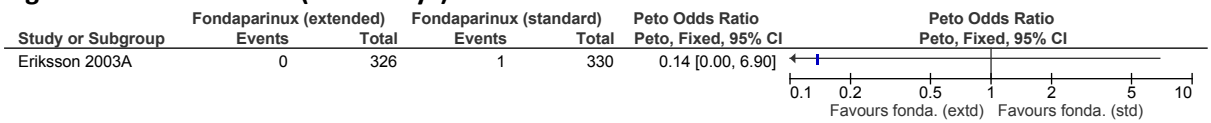


Figure 237: Fatal PE (25-31 days)



L.22.8 UFH versus no prophylaxis

Figure 238: All-cause mortality (time-point not reported)

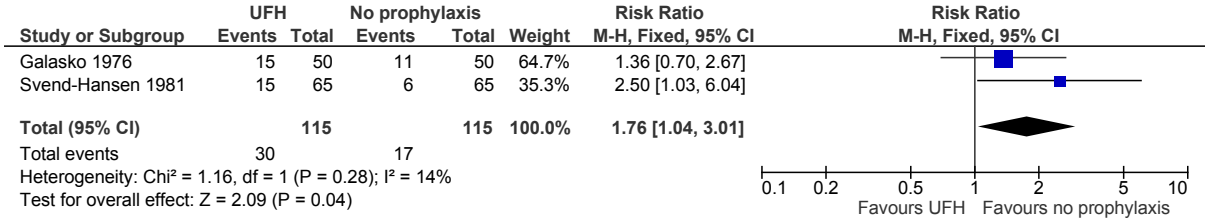


Figure 239: DVT (symptomatic and asymptomatic) (14 days)

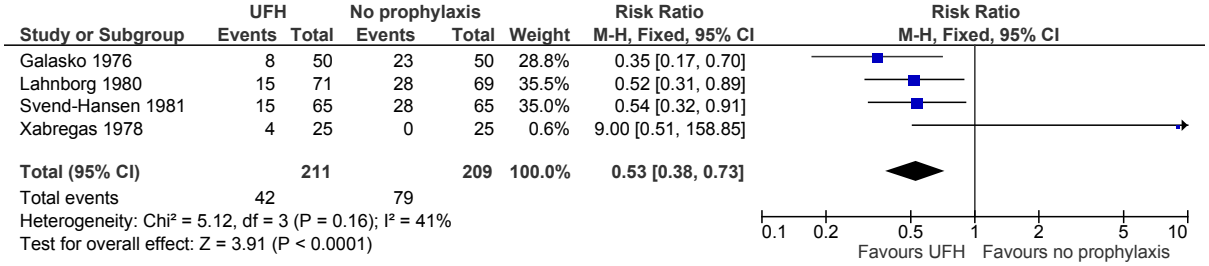


Figure 240: PE (time-point not reported)

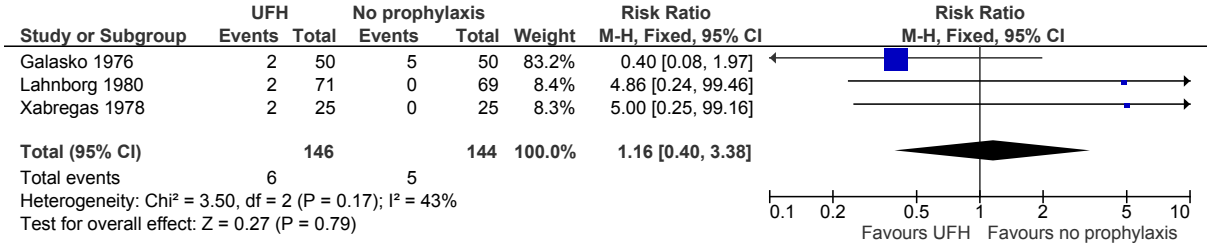
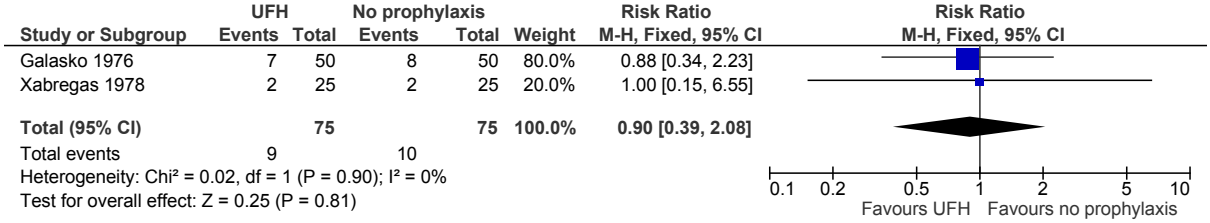


Figure 241: Fatal PE (time-point not reported)

Figure 242: Wound infection (time-point not reported)



L.22.9 UFH + AES (length unspecified) versus AES (length unspecified)

Figure 243: All-cause mortality (time-point not reported)

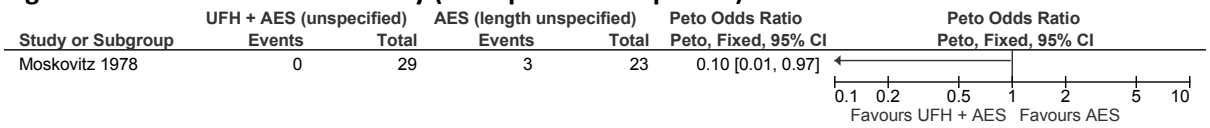


Figure 244: DVT (symptomatic and asymptomatic) (10 days)

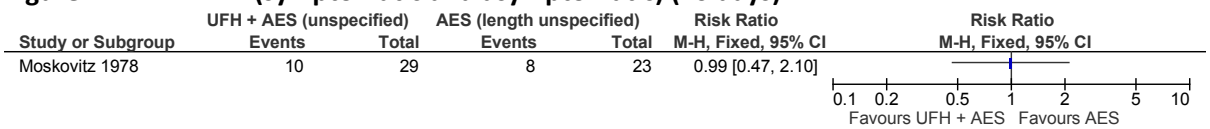


Figure 245: PE (time-point not reported)

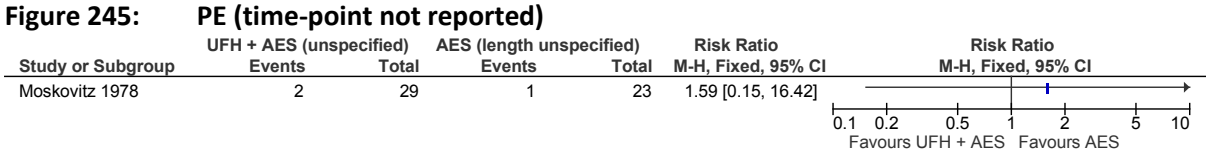


Figure 246: Major bleeding (time-point not reported)

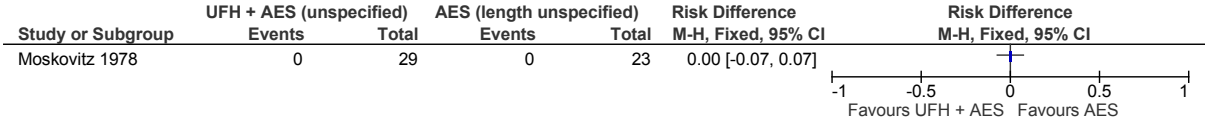
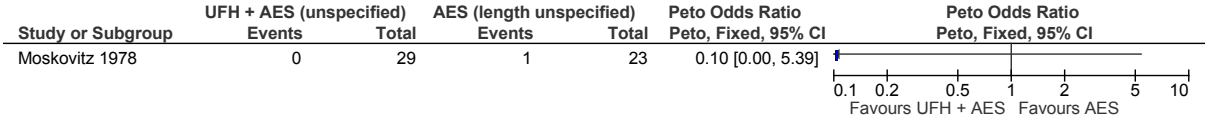


Figure 247: Fatal PE (time-point not reported)



L.22.10 VKA versus no prophylaxis

Figure 248: All-cause mortality (90 days)

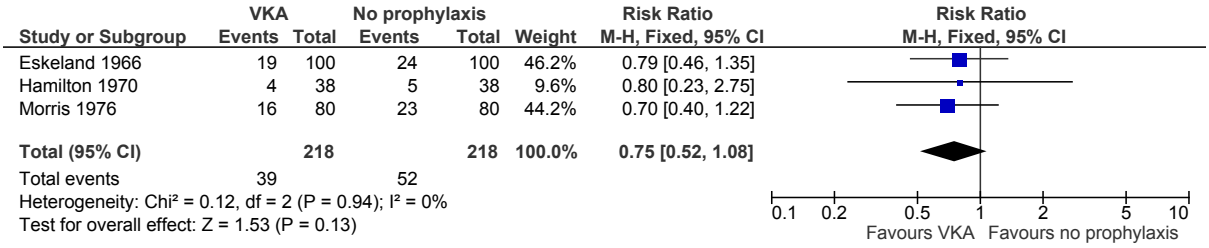


Figure 249: DVT (symptomatic and asymptomatic) (10 days)

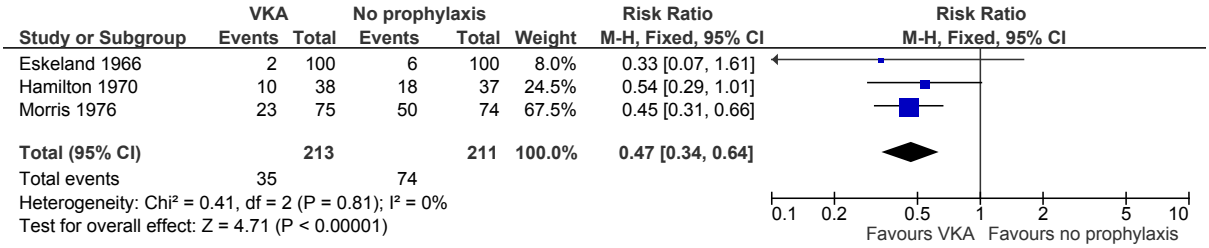


Figure 250: PE (90 days)

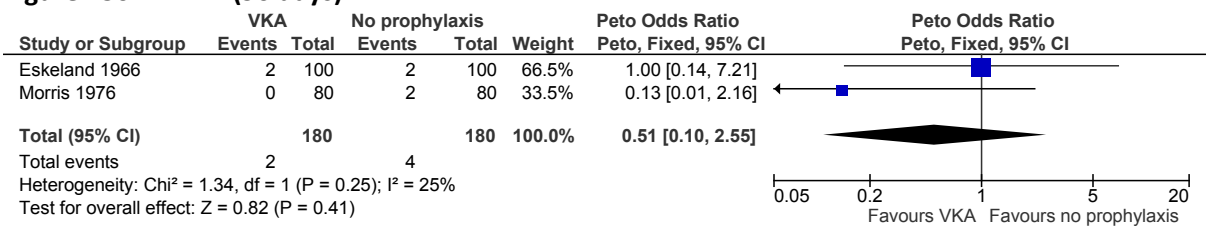


Figure 251: Major bleeding (time-point not reported)

Study or Subgroup	VKA Events	VKA Total	No prophylaxis Events	No prophylaxis Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hamilton 1970	11	38	9	38	81.8%	1.22 [0.57, 2.61]
Morris 1976	8	80	2	80	18.2%	4.00 [0.88, 18.26]
Total (95% CI)		**118**		**118**	**100.0%**	**1.73 [0.88, 3.37]**
Total events	19		11			

Heterogeneity: Chi² = 1.98, df = 1 (P = 0.16); I² = 49%
Test for overall effect: Z = 1.60 (P = 0.11)

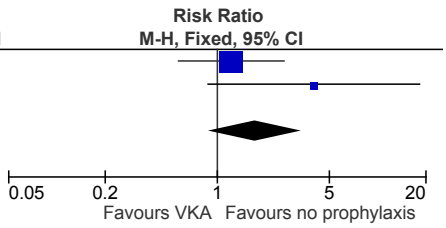


Figure 252: Fatal PE (90 days)

Study or Subgroup	VKA Events	VKA Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Eskeland 1966	1	100	7	100	0.14 [0.02, 1.14]

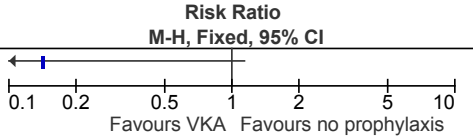
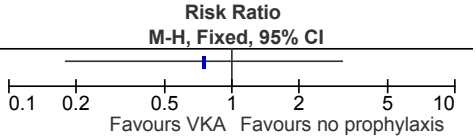


Figure 253: Deep wound infection (time-point not reported)

Study or Subgroup	VKA Events	VKA Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Hamilton 1970	3	38	4	38	0.75 [0.18, 3.13]



L.22.11 Aspirin (± other prophylaxis) versus no aspirin (± other prophylaxis)

Figure 254: All-cause mortality (35 days)

Study or Subgroup	Aspirin Events	Aspirin Total	No aspirin Events	No aspirin Total	Risk Ratio M-H, Fixed, 95% CI
PEP 2000	447	6679	461	6677	0.97 [0.85, 1.10]

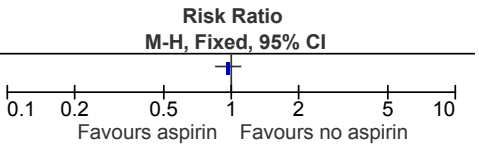


Figure 255: PE (35 days)

Study or Subgroup	Aspirin Events	Aspirin Total	No aspirin Events	No aspirin Total	Risk Ratio M-H, Fixed, 95% CI
PEP 2000	28	6679	38	6677	0.74 [0.45, 1.20]

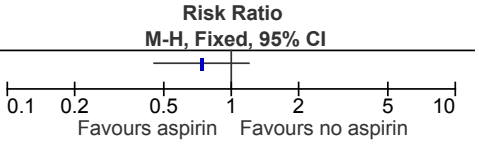


Figure 256: Fatal PE (35 days)

Study or Subgroup	Aspirin Events	Aspirin Total	No aspirin Events	No aspirin Total	Risk Ratio M-H, Fixed, 95% CI
PEP 2000	18	6679	43	6677	0.42 [0.24, 0.72]

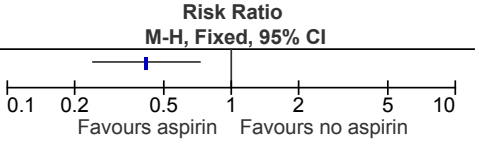
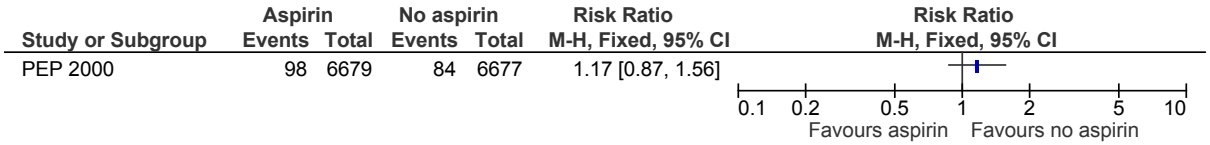
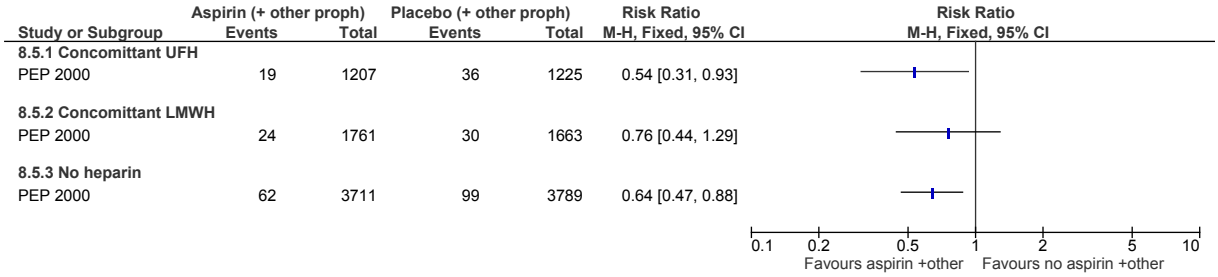


Figure 257: Wound infection (35 days)



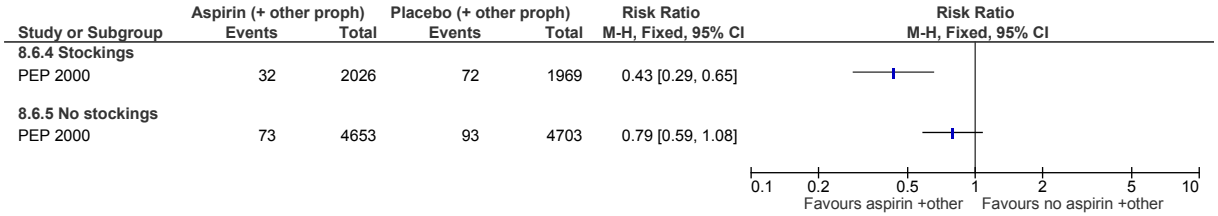
L.22.11.1 Sub-group analysis (not pre-specified) for concomitant prophylaxis treatments in the PEP aspirin trial

Figure 258: Concomitant heparin treatment – Combination PE and DVT outcome



Note: This sub-group data was presented for information only to the committee to inform discussion around the indirectness of the intervention and outcome. This data was not formally analysed via GRADE or included in the body of evidence under consideration. No information provided on the proportion of people with heparin who also had AES.

Figure 259: Concomitant AES – Combination PE and DVT outcome



Note: This sub-group data was presented for information only to the committee to inform discussion around the indirectness of the intervention and outcome. This data was not formally analysed via GRADE or included in the body of evidence under consideration. No information provided on the proportion of people with AES who also had heparin.

L.22.12 IPCD (thigh-length) versus no prophylaxis

Figure 260: DVT (symptomatic and asymptomatic (mean: 14 days)

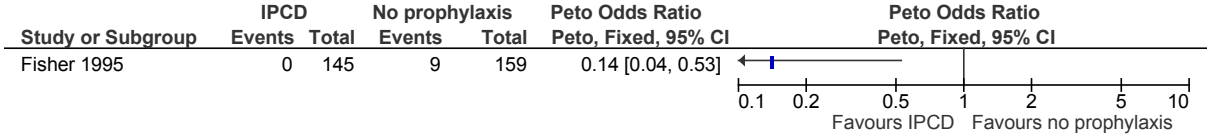
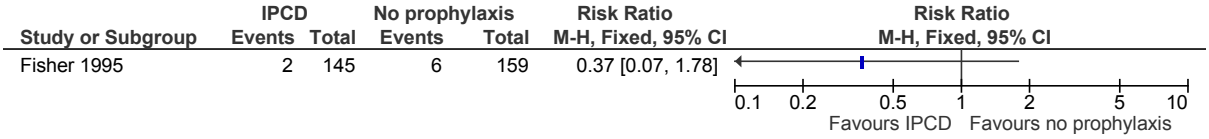


Figure 261: PE (5-10 days)



L.23 Elective hip replacement

L.23.1 LMWH (standard dose; standard duration) versus no prophylaxis

Figure 262: DVT (symptomatic and asymptomatic) (11 days)

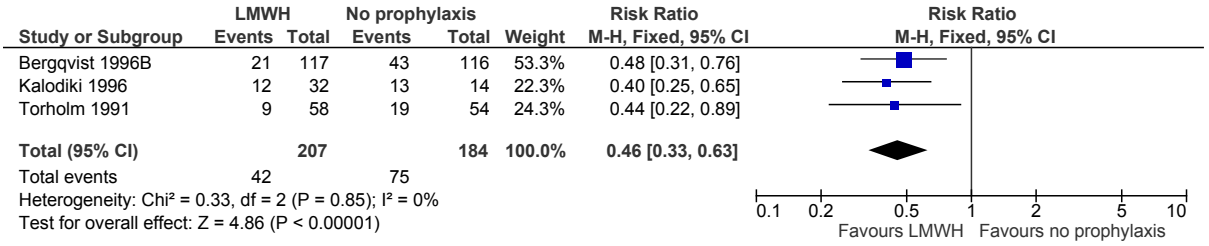


Figure 263: PE (11 days)

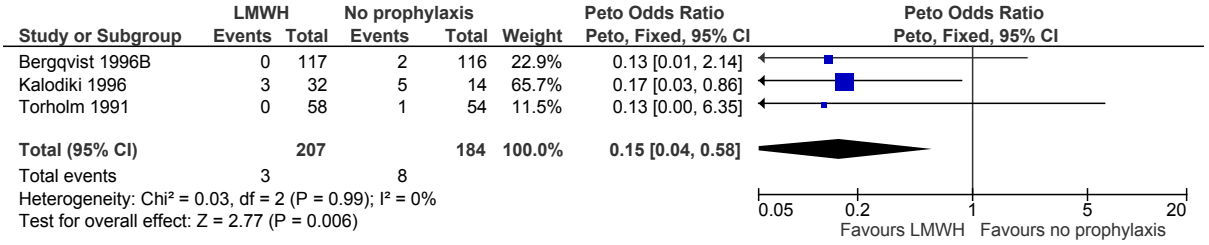


Figure 264: Wound infection (time-point not reported)

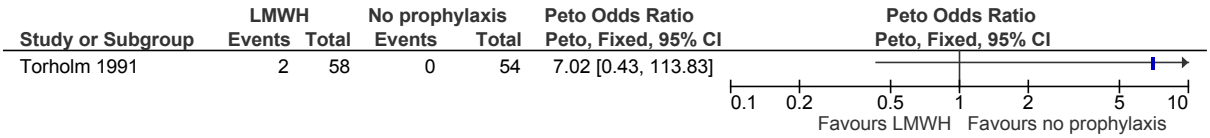
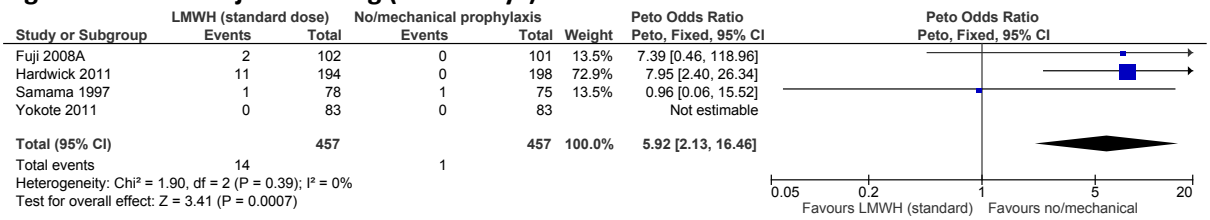
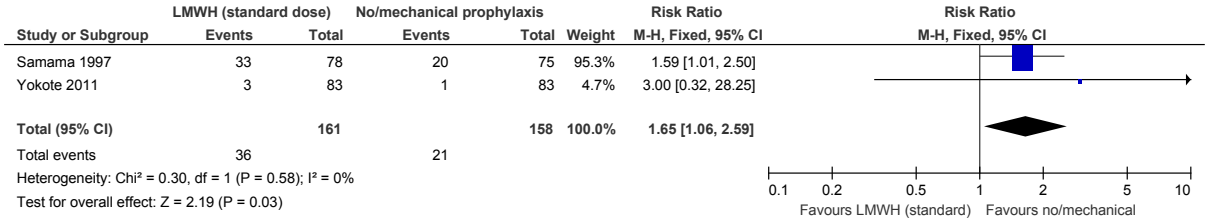


Figure 265: Major bleeding (10-12 days)



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

Figure 266: Wound haematoma (11-12 days)



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

L.23.2 LMWH (standard dose; standard duration) versus UFH

Figure 267: All-cause mortality (7 days)

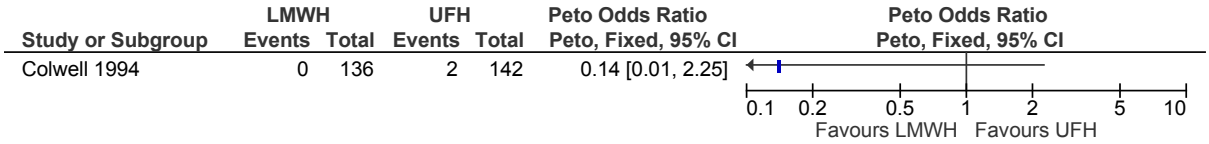


Figure 268: DVT (symptomatic and asymptomatic) (7-14 days)

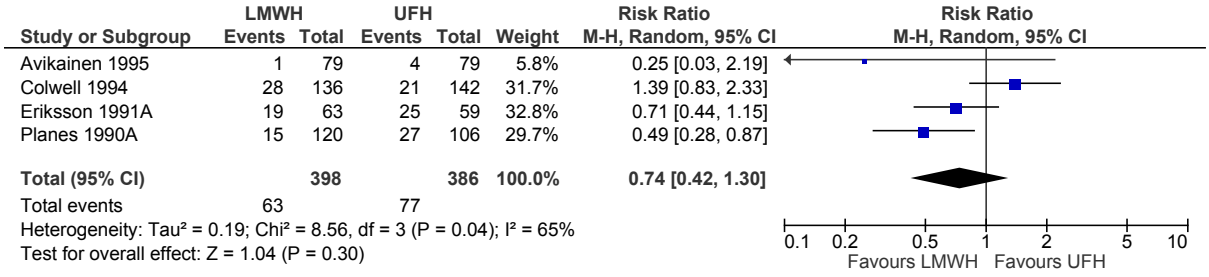


Figure 269: PE (7 days)

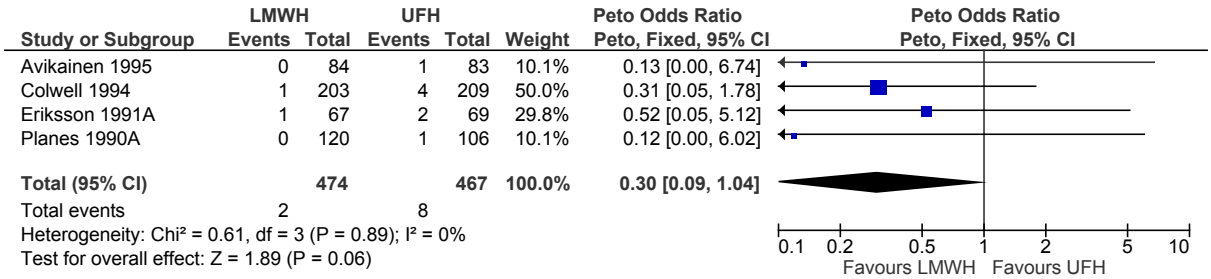


Figure 270: Major bleeding (7 days)

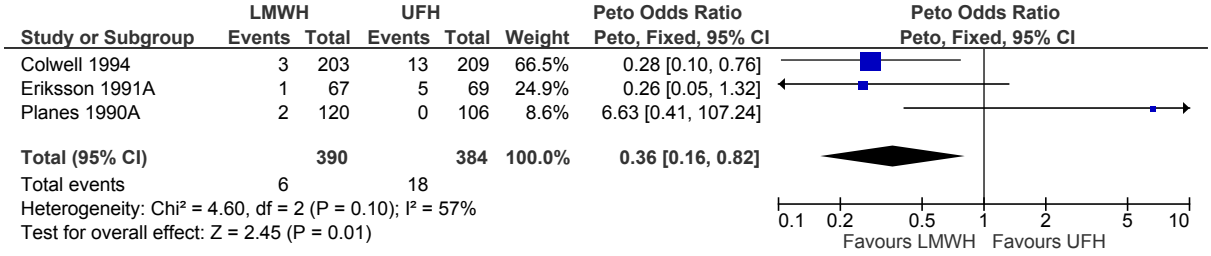
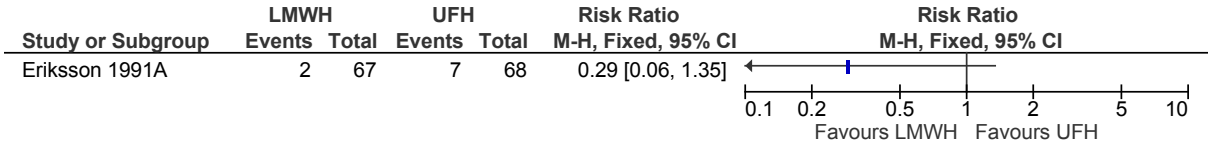


Figure 271: Wound haematoma (time-point not reported)



L.23.3 LMWH (standard dose; standard duration) versus VKA

Figure 272: DVT (symptomatic and asymptomatic (9 days)

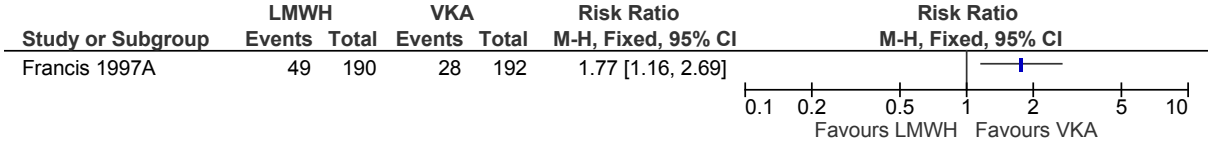


Figure 273: Major bleeding (9 days)

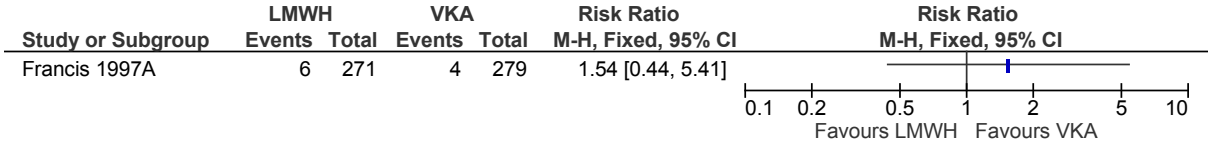
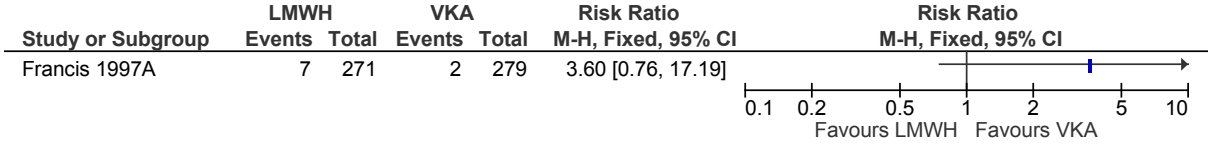


Figure 274: Wound haematoma (9 days)



L.23.4 LMWH (standard dose; standard duration) versus dabigatran

Figure 275: All-cause mortality (28-35 days)

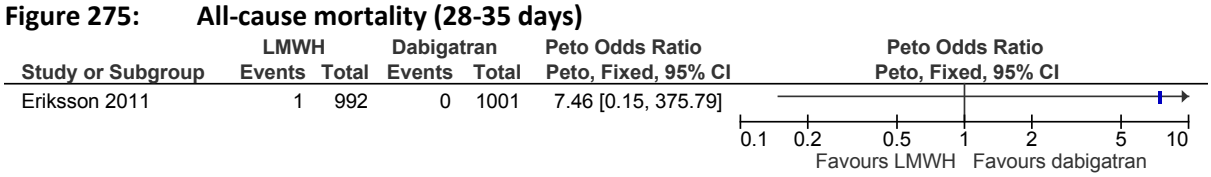


Figure 276: DVT (symptomatic and asymptomatic) (28-35 days)

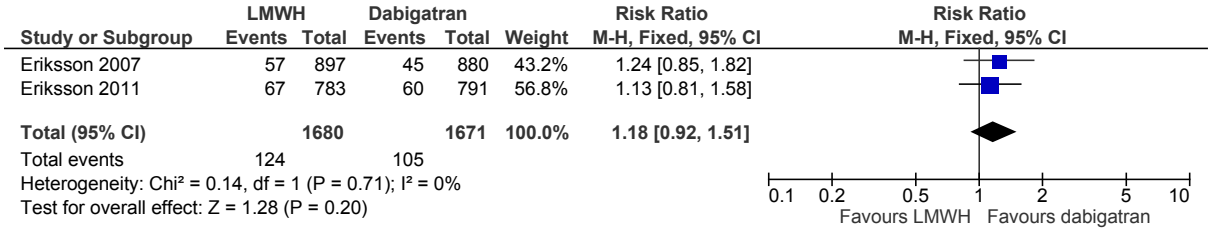


Figure 277: PE (28-35 days)

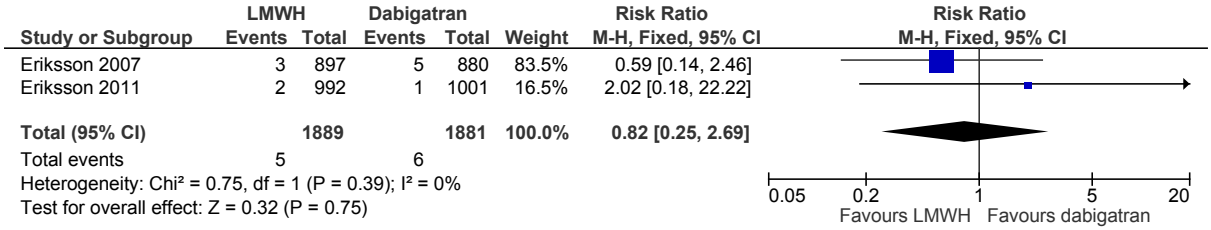


Figure 278: Major bleeding (28-35 days)

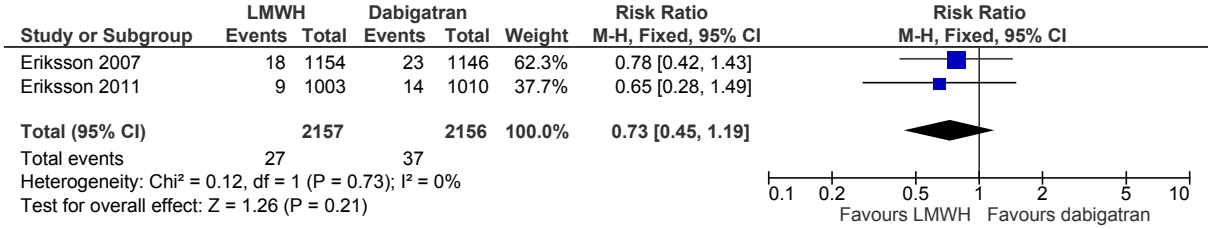
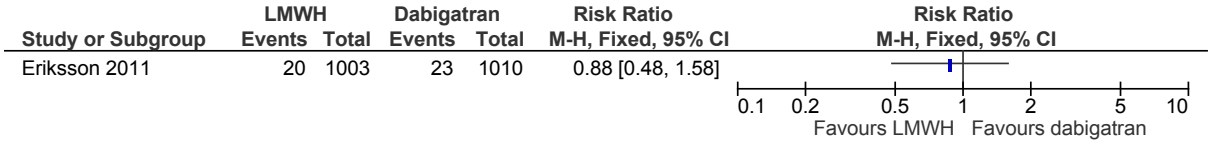


Figure 279: Clinically relevant non-major bleeding (28-35 days)



L.23.5 LMWH (standard dose; standard duration) versus apixaban

Figure 280: All-cause mortality (32-38 days)

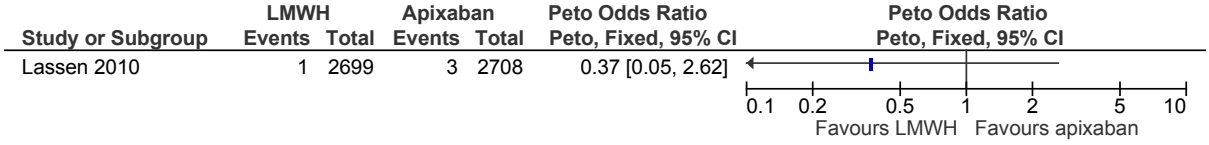


Figure 281: DVT (symptomatic and asymptomatic) (32-38 days)

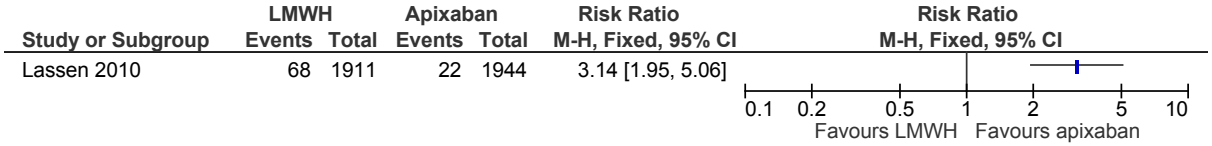


Figure 282: PE (32-38 days)

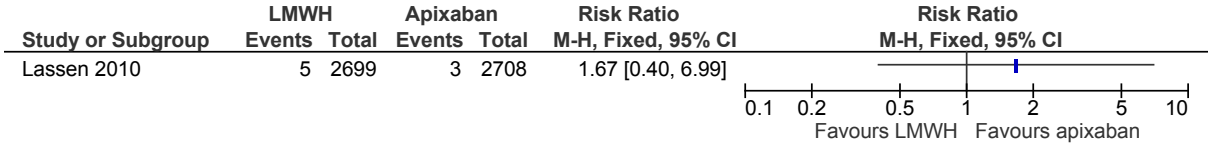


Figure 283: Major bleeding (32-38 days)

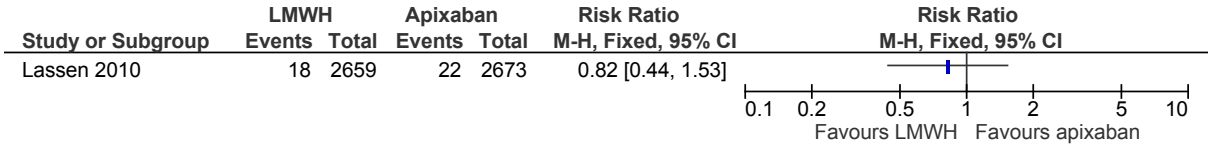


Figure 284: Fatal PE (32-38 days)

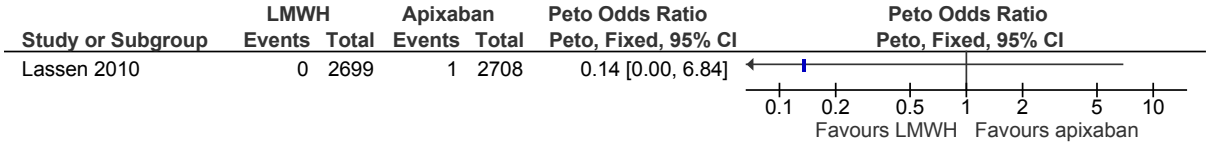


Figure 285: Clinically relevant non-major bleeding (32-38 days)

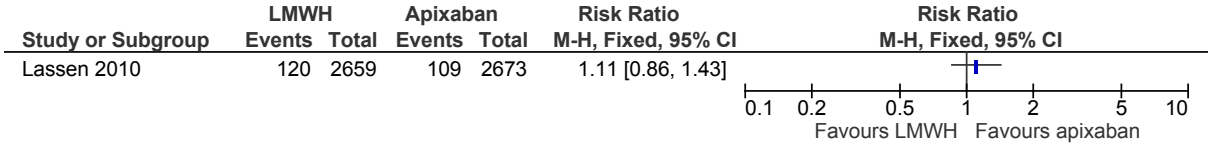
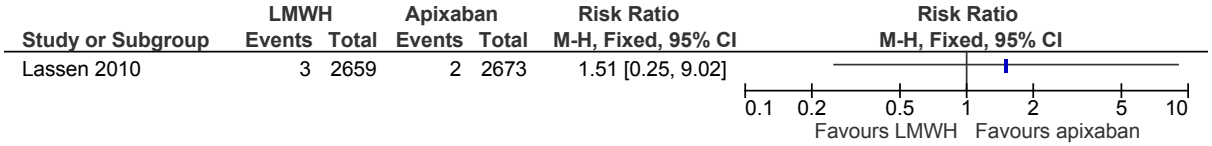


Figure 286: Heparin-induced thrombocytopenia (32-38 days)



L.23.6 LMWH (standard dose; standard duration) versus rivaroxaban

Figure 287: All-cause mortality (30-42 days)

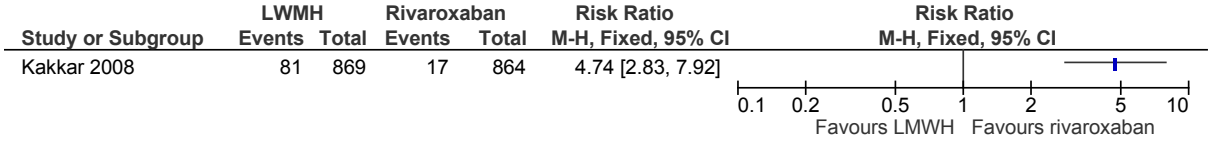


Figure 288: DVT (symptomatic and asymptomatic) (32-40 days)

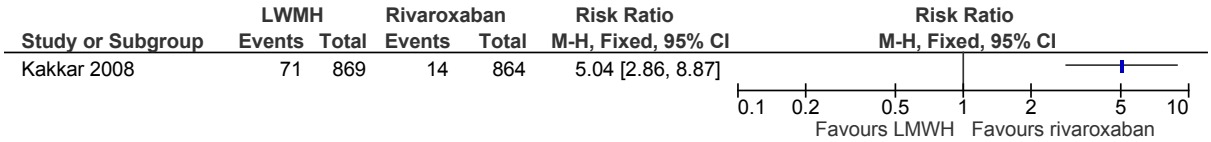


Figure 289: PE (32-40 days)

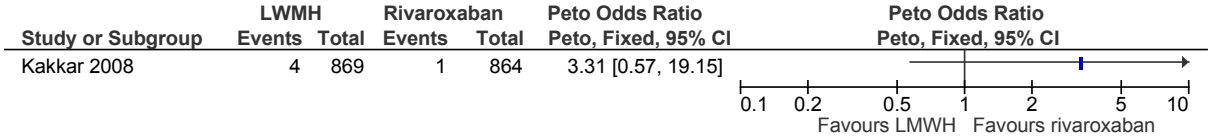


Figure 290: Major bleeding (41 days)

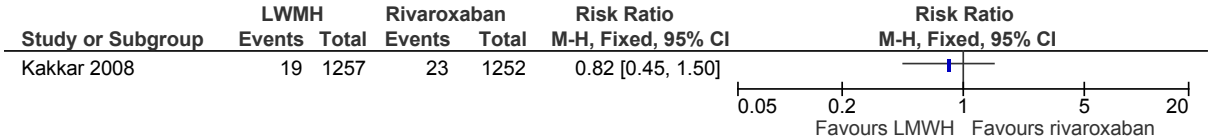


Figure 291: Clinically relevant non-major bleeding (41 days)

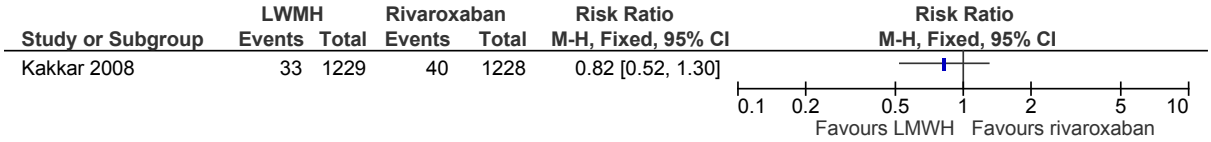
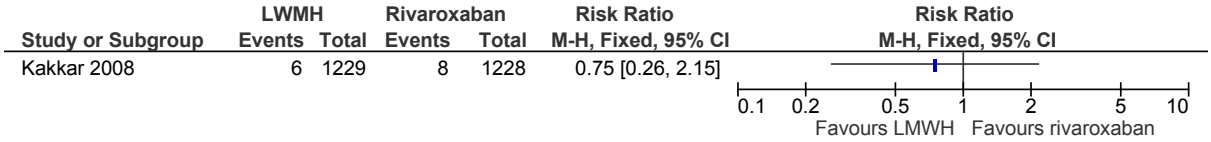


Figure 292: Wound infection (41 days)



L.23.7 LMWH (standard dose; standard duration) versus IPCD

Figure 293: DVT (symptomatic and asymptomatic) (84 days)

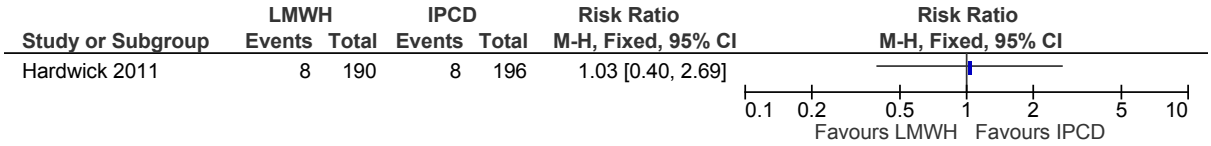
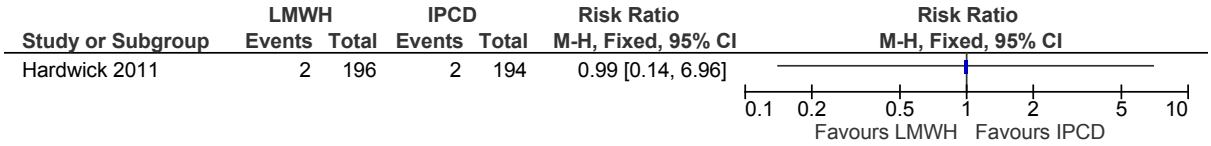


Figure 294: PE (time-point not reported)



L.23.8 LMWH (standard dose; standard duration) + AES versus no prophylaxis

Figure 295: DVT (symptomatic and asymptomatic) (8-12 days)

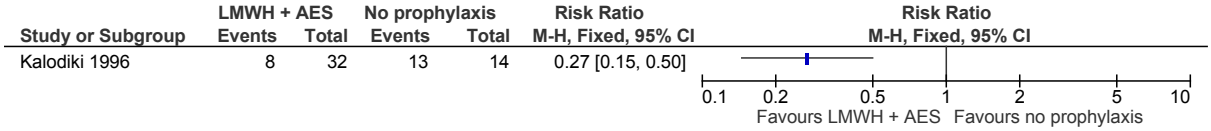
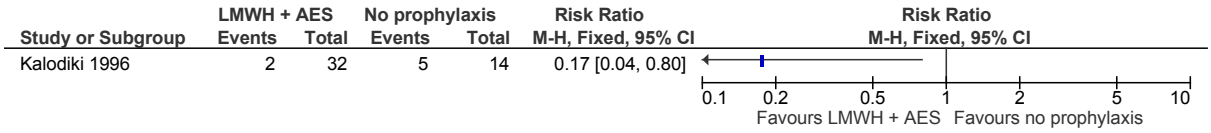


Figure 296: PE (8-12 days)



L.23.9 LMWH (standard dose; standard duration) + AES versus AES alone

Figure 297: All-cause mortality (90 days)

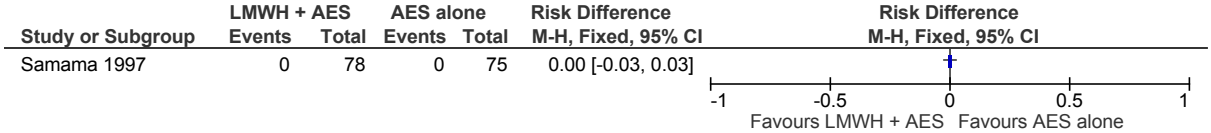


Figure 298: DVT (symptomatic and asymptomatic) (time-point not reported)

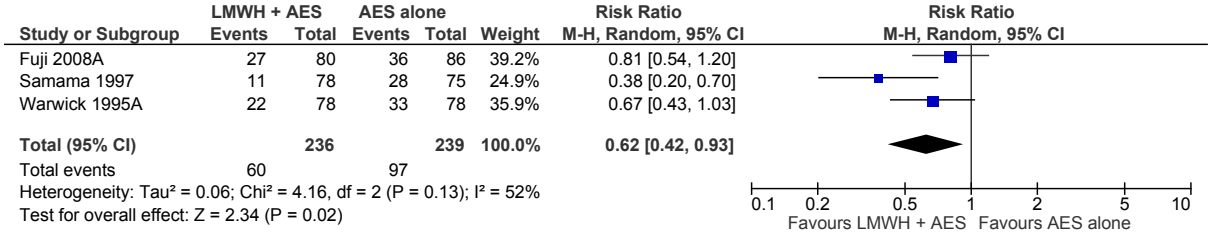
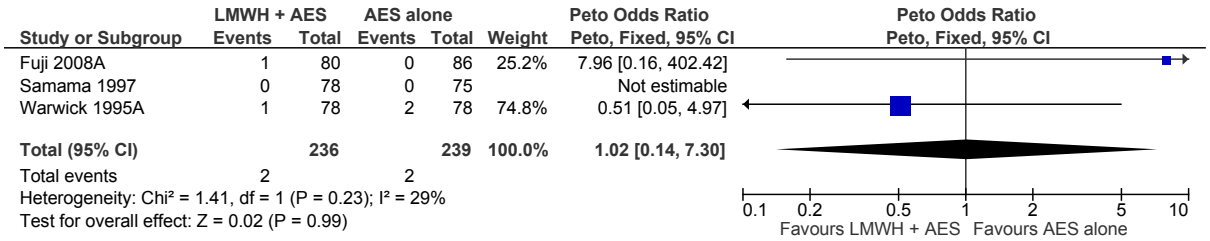


Figure 299: PE (90 days)



L.23.10 LMWH (standard dose; standard duration) + IPCD + AES versus IPCD + AES

Figure 300: DVT (symptomatic and asymptomatic) (11 days)

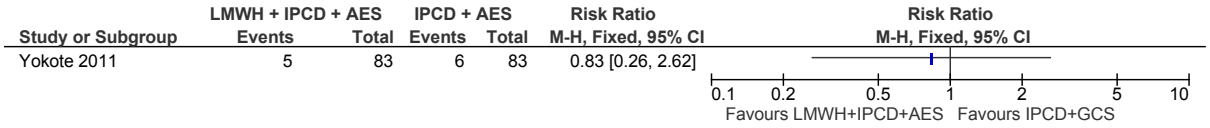
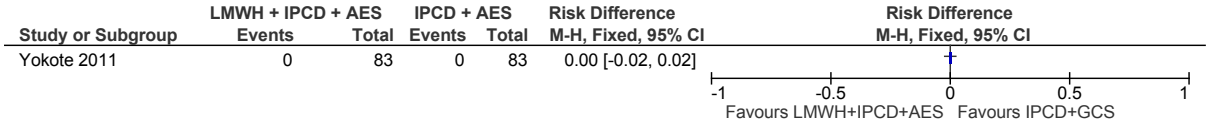


Figure 301: PE (11 days)



L.23.11 LMWH (standard dose; standard duration) + AES versus LMWH (standard dose)

Figure 302: DVT (symptomatic and asymptomatic) (8-12 days)

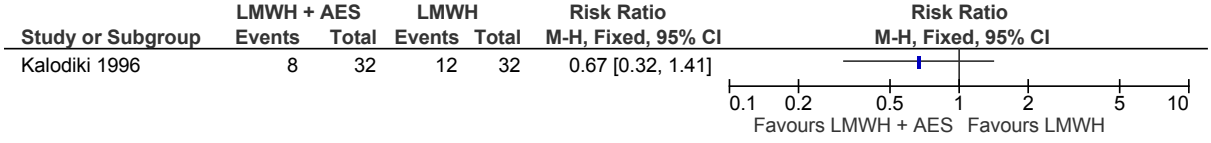
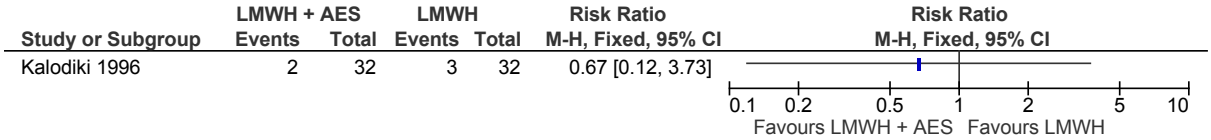
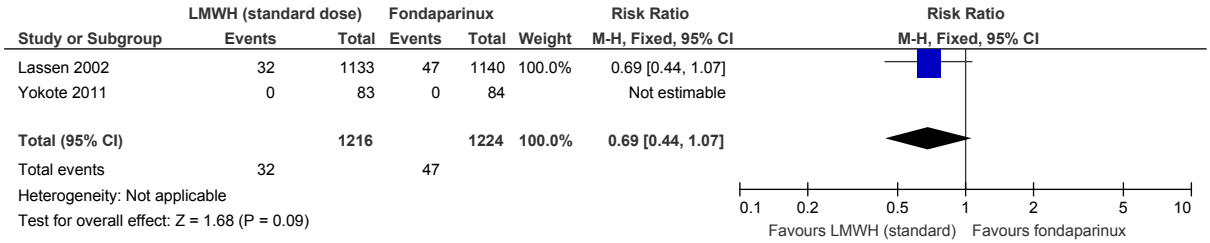


Figure 303: PE (8-12 days)



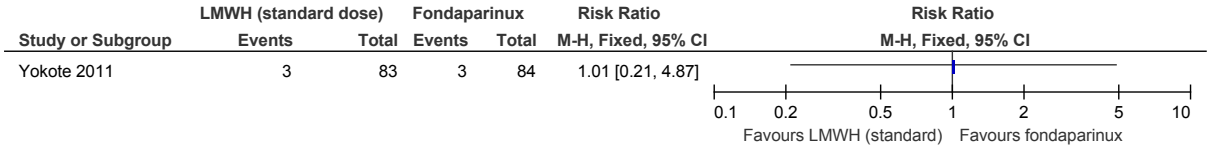
L.23.12 LMWH (standard dose; standard duration) versus fondaparinux

Figure 304: Major bleeding (11-49 days)



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

Figure 305: Wound haematoma (11 days)



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

L.23.13 LMWH (standard dose; standard duration) + AES versus fondaparinux + AES

Figure 306: All-cause mortality (49 days)

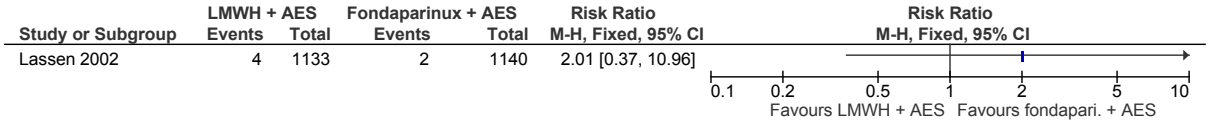


Figure 307: DVT (symptomatic and asymptomatic) (49 days)

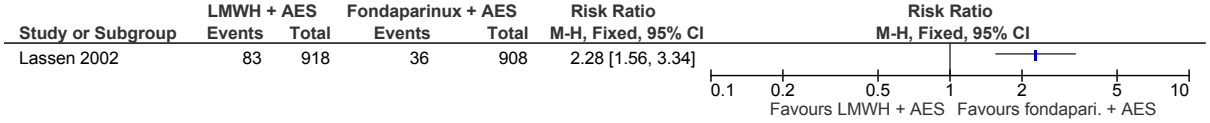


Figure 308: PE (49 days)

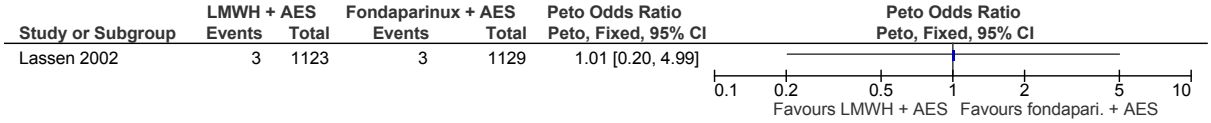
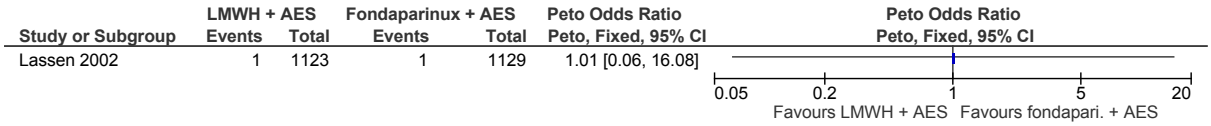


Figure 309: Fatal PE (49 days)



L.23.14 LMWH (standard dose) + IPCD + AES versus fondaparinux + IPCD + AES

Figure 310: DVT (symptomatic and asymptomatic) (11 days)

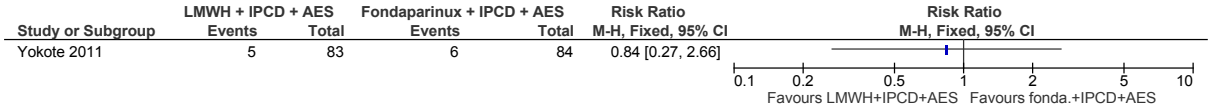
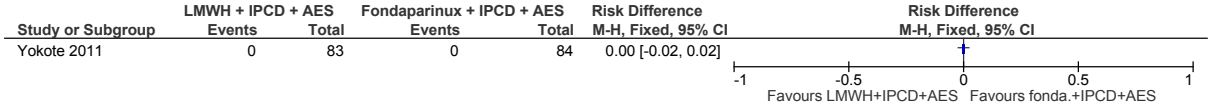


Figure 311: PE (11 days)



L.23.15 LMWH (standard dose; standard duration) versus foot pump

Figure 312: DVT (symptomatic and asymptomatic) (90 days)

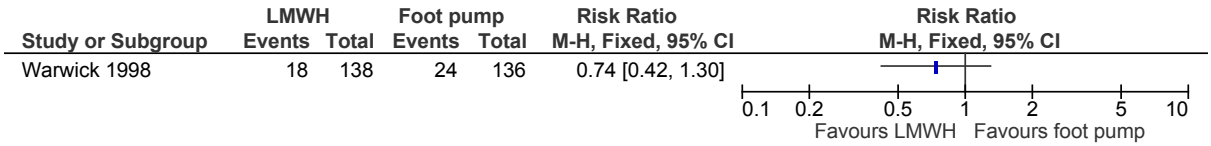


Figure 313: PE (90 days)

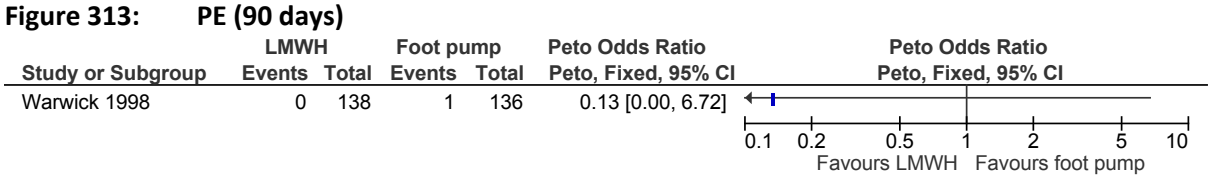
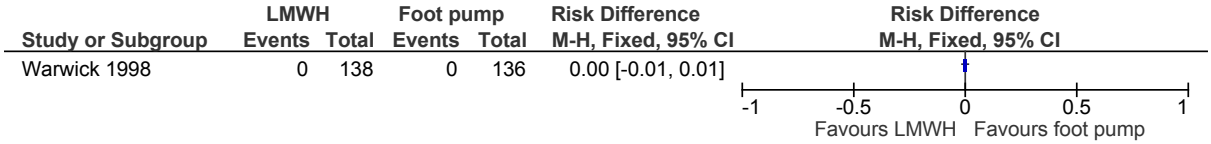


Figure 314: Fatal PE (90 days)



L.23.16 LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)

Figure 315: All-cause mortality (27-29 days)

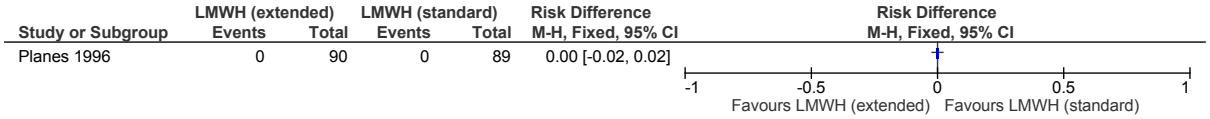


Figure 316: DVT (symptomatic and asymptomatic) (23-35 days)

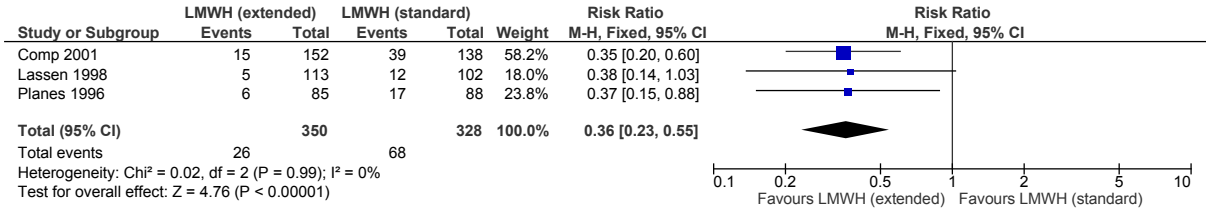


Figure 317: PE (23-35 days)

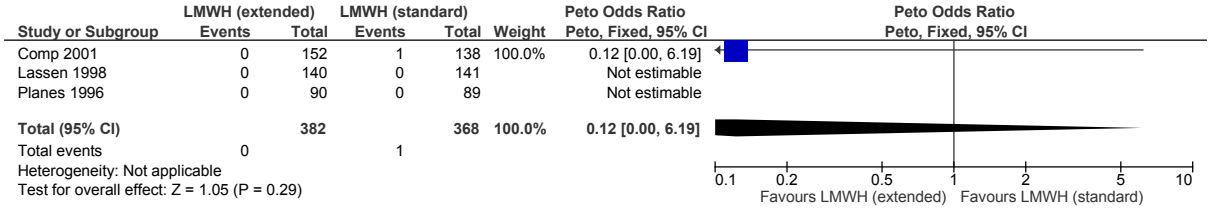


Figure 318: Major bleeding (23-25 days)

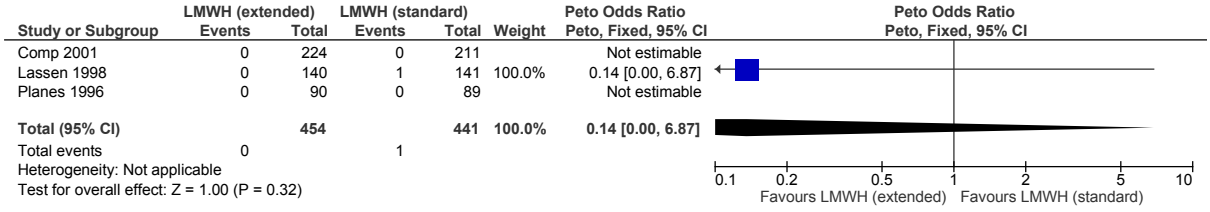


Figure 319: Heparin-induced thrombocytopenia (27-29 days)

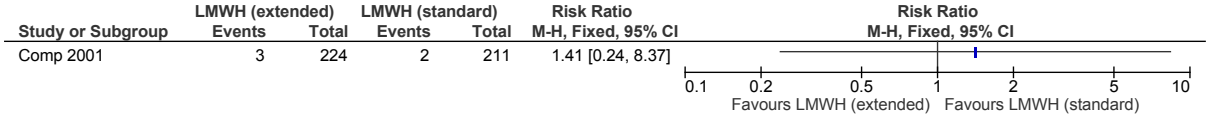
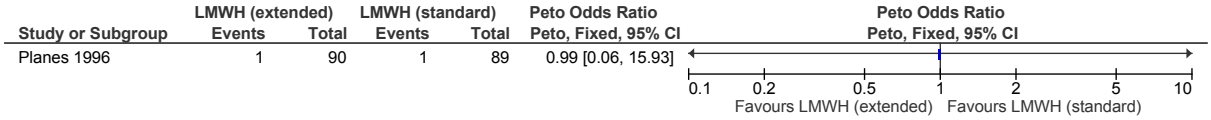


Figure 320: Wound haematoma (27-29 days)



L.23.17 LMWH (standard dose; extended duration) + AES versus LMWH (standard dose; standard duration) + AES

Figure 321: DVT (symptomatic and asymptomatic) (23-35 days)

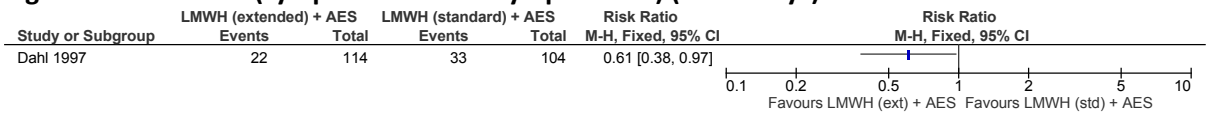
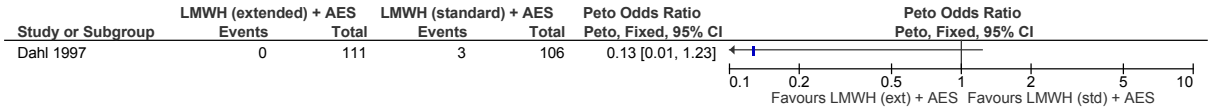


Figure 322: PE (23-35 days)



L.23.18 LMWH (standard dose; extended duration) versus rivaroxaban

Figure 323: All-cause mortality (mean: 70 days)

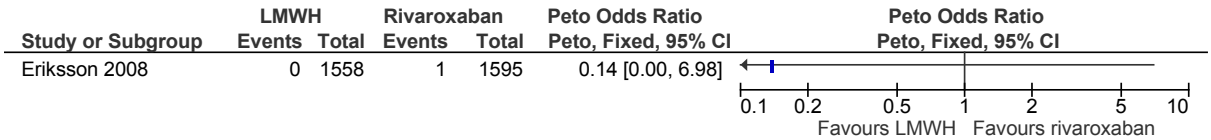


Figure 324: DVT (symptomatic and asymptomatic) (mean: 36 days)

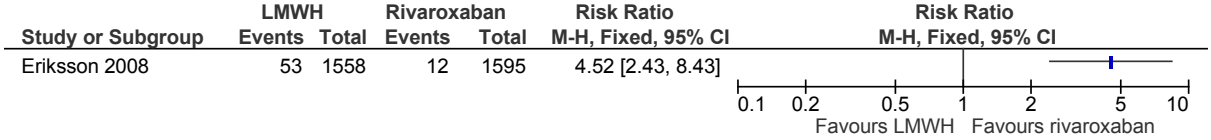


Figure 325: PE (mean: 36 days)

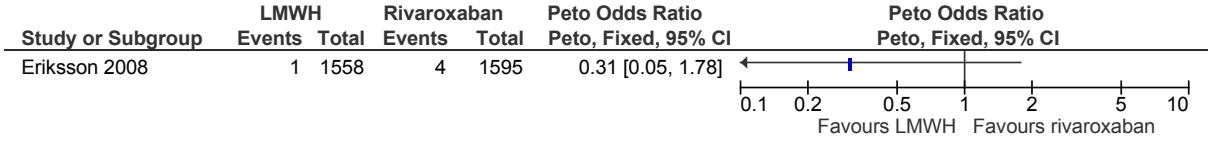


Figure 326: Major bleeding (mean: 38 days)

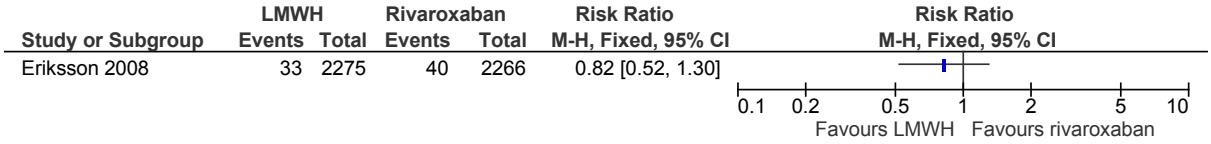


Figure 327: Clinically relevant non-major bleeding (mean: 38 days)

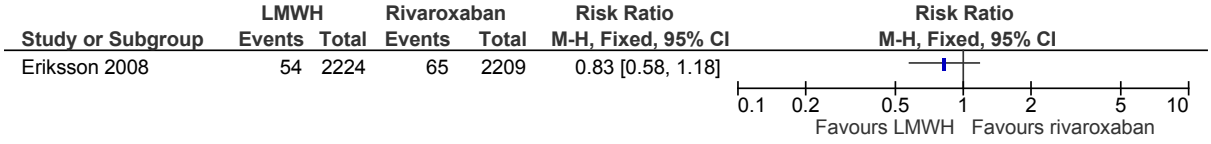
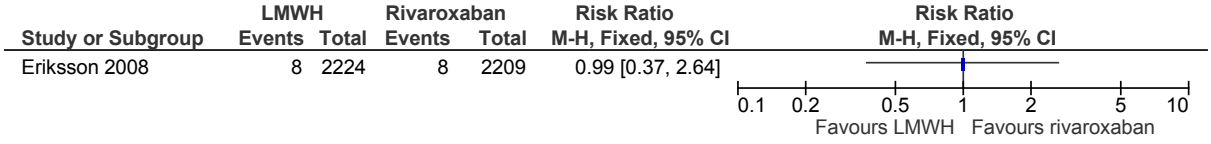


Figure 328: Wound infection (mean: 38 days)



L.23.19 LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration) followed by aspirin (extended duration)

Figure 329: All-cause mortality (90 days)

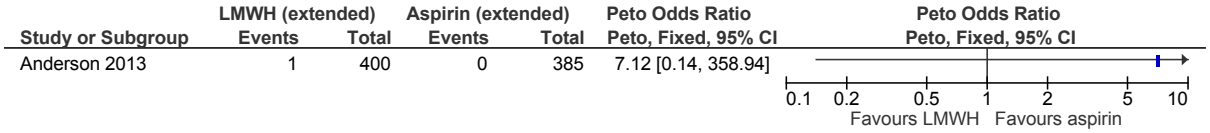


Figure 330: PE (90 days)

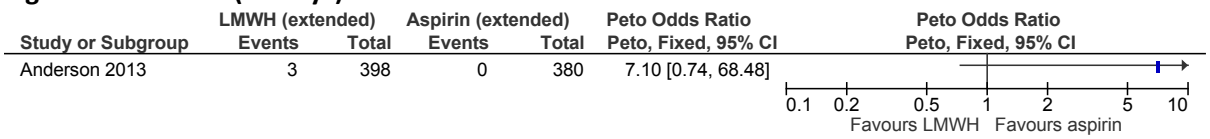


Figure 331: Fatal PE (90 days)

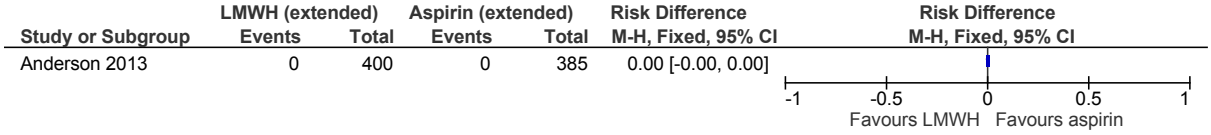


Figure 332: Major bleeding (90 days)

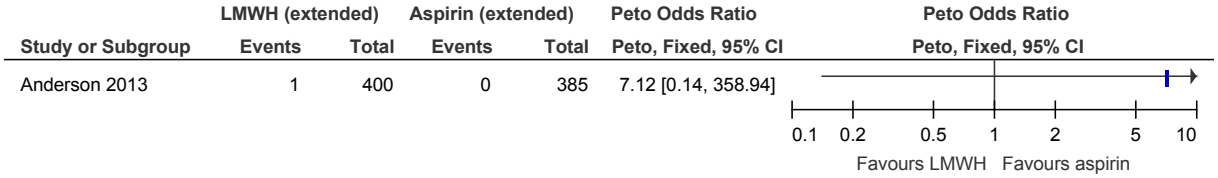


Figure 333: Clinically relevant non-major bleeding (90 days)

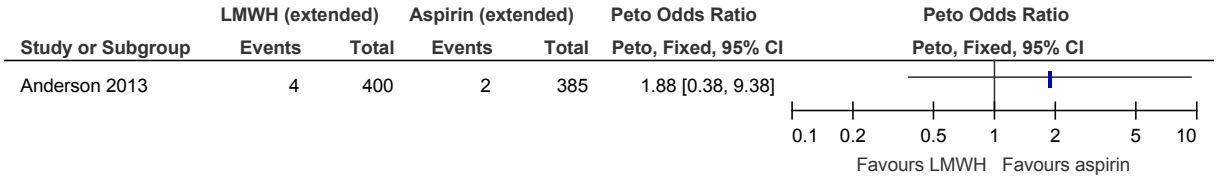
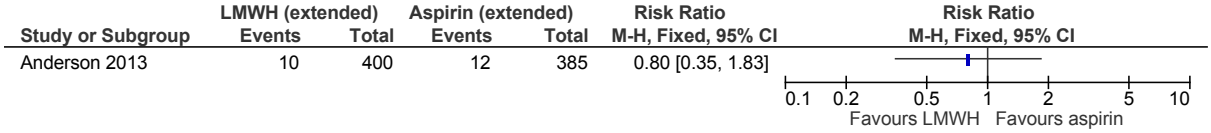


Figure 334: Wound infection (90 days)



L.23.20 LMWH (high dose; standard duration) versus no prophylaxis

Figure 335: DVT (symptomatic and asymptomatic) (11 days)

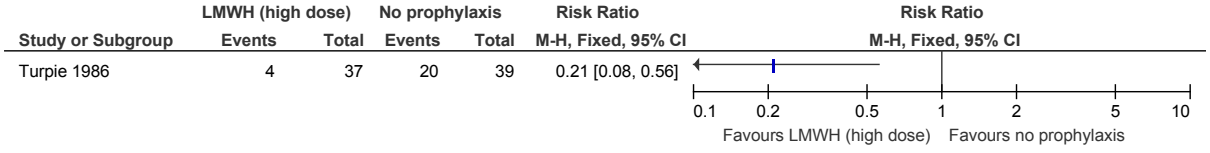


Figure 336: PE (11 days)

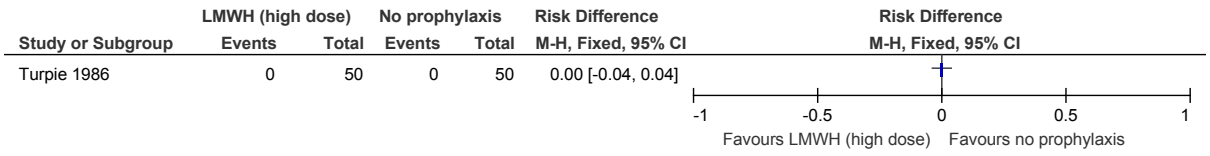
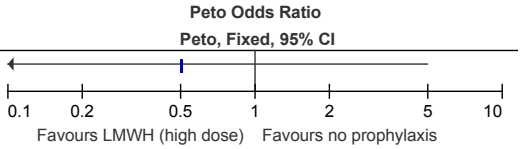


Figure 337: Major bleeding (11 days)

Study or Subgroup	LMWH (high dose) Events	Total	No prophylaxis Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Turpie 1986	1	50	2	50	0.51 [0.05, 4.98]



L.23.21 LMWH (high dose; standard duration) versus UFH

Figure 338: All-cause mortality (7 days)

Study or Subgroup	LMWH (high dose) Events	Total	UFH Events	Total	Risk Ratio M-H, Fixed, 95% CI
Colwell 1994	7	136	2	142	3.65 [0.77, 17.28]

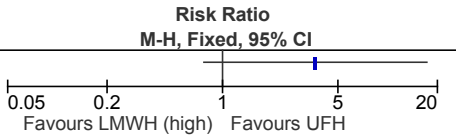


Figure 339: DVT (symptomatic and asymptomatic) (10-14 days)

Study or Subgroup	LMWH (high dose) Events	Total	UFH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Colwell 1994	8	136	21	142	25.7%	0.40 [0.18, 0.87]
Kakkar 2000	9	101	24	116	28.0%	0.43 [0.21, 0.88]
Levine 1991	50	258	61	263	46.2%	0.84 [0.60, 1.16]
Total (95% CI)		**495**		**521**	**100.0%**	**0.57 [0.33, 0.98]**
Total events	67		106			

Heterogeneity: Tau² = 0.13; Chi² = 4.91, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 2.03 (P = 0.04)

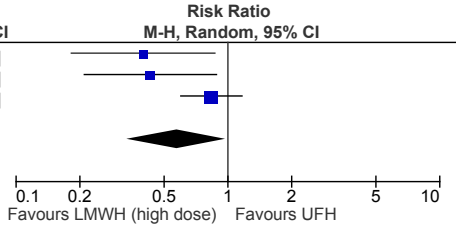


Figure 340: PE (10-14 days)

Study or Subgroup	LMWH (high dose) Events	Total	UFH Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Colwell 1994	0	195	4	209	44.4%	0.14 [0.02, 1.02]
Kakkar 2000	1	125	2	134	33.3%	0.55 [0.06, 5.32]
Levine 1991	1	332	1	333	22.3%	1.00 [0.06, 16.07]
Total (95% CI)		**652**		**676**	**100.0%**	**0.35 [0.09, 1.28]**
Total events	2		7			

Heterogeneity: Chi² = 1.50, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.59 (P = 0.11)

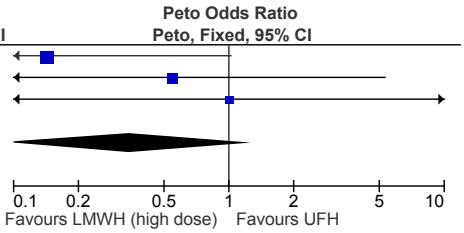


Figure 341: Major bleeding (10-14 days)

Study or Subgroup	LMWH (high dose) Events	Total	UFH Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Colwell 1994	8	195	13	209	39.7%	0.66 [0.28, 1.56]
Levine 1991	11	333	19	332	60.3%	0.58 [0.28, 1.19]
Total (95% CI)		**528**		**541**	**100.0%**	**0.61 [0.35, 1.06]**
Total events	19		32			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.75 (P = 0.08)

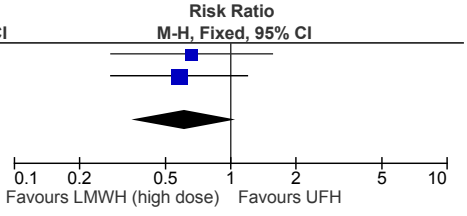


Figure 342: Fatal PE (28 days)

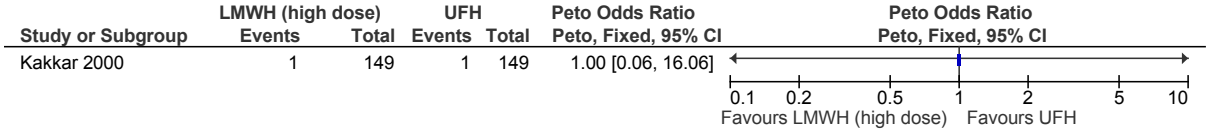
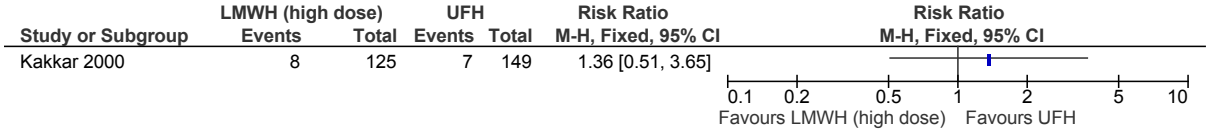


Figure 343: Wound haematoma (28 days)



L.23.22 LMWH (high dose; standard duration) versus LMWH (standard dose; standard duration)

Figure 344: All-cause mortality (7 days)

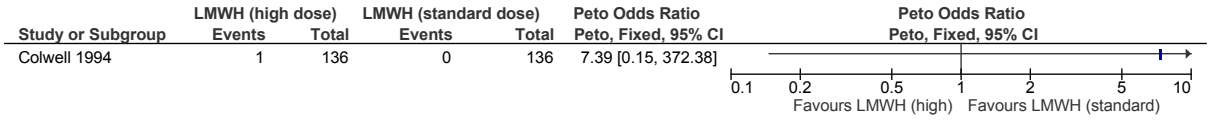


Figure 345: DVT (symptomatic and asymptomatic) (15 days)

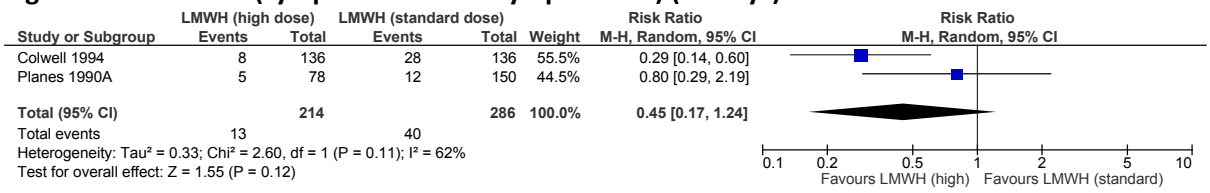


Figure 346: PE (7 days)

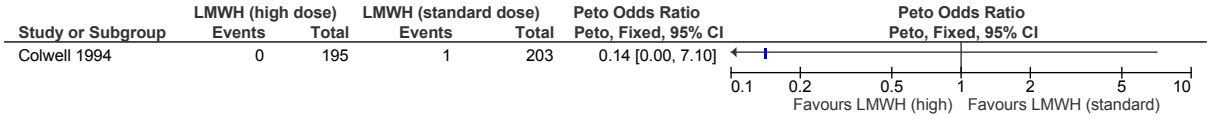


Figure 347: Major bleeding (7 days)

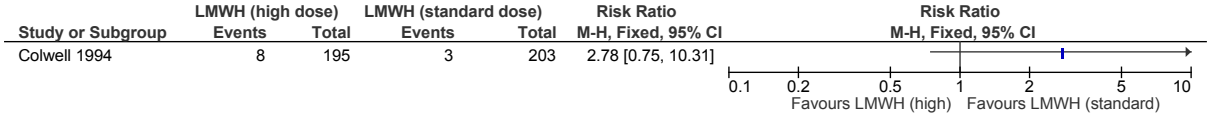
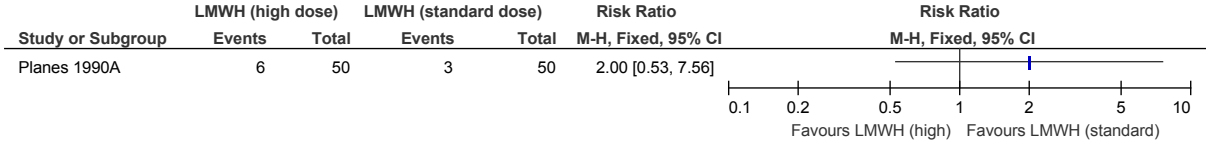
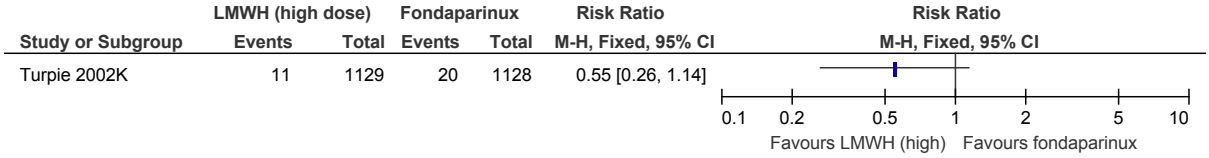


Figure 348: Wound haematoma (15 days)



L.23.23 LMWH (high dose; standard duration) versus fondaparinux

Figure 349: **Major bleeding (49 days)**



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

L.23.24 LMWH (high dose; standard duration) + AES versus fondaparinux + AES

Figure 350: All-cause mortality (49 days)

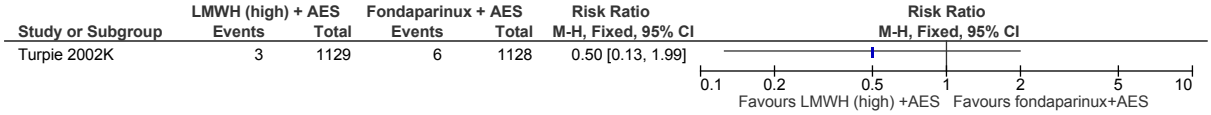


Figure 351: DVT (symptomatic and asymptomatic) (49 days)

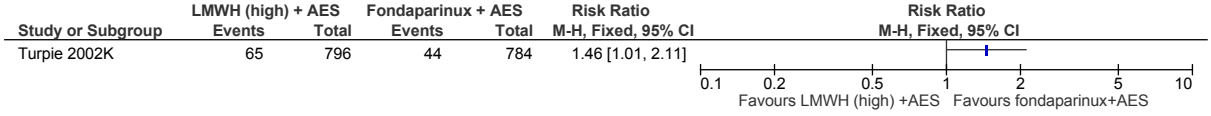


Figure 352: PE (49 days)

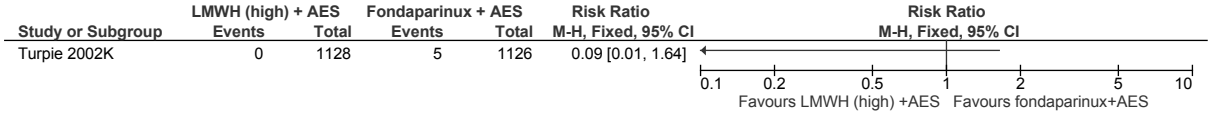
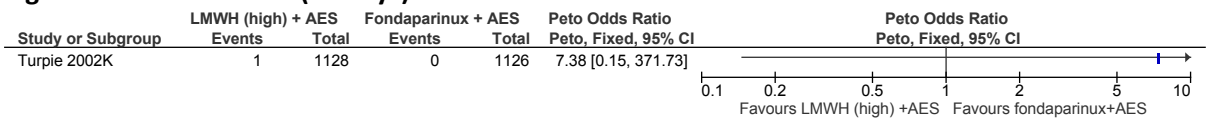


Figure 353: Fatal PE (49 days)



L.23.25 LMWH (high dose; standard duration) versus VKA

Figure 354: All-cause mortality (90 days)

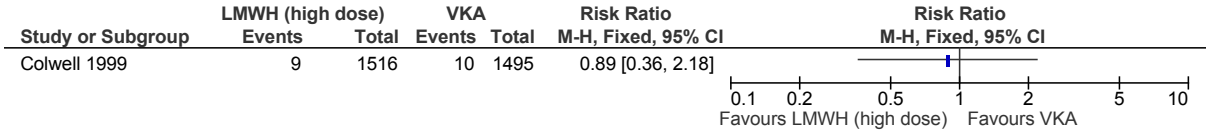


Figure 355: PE (90 days)

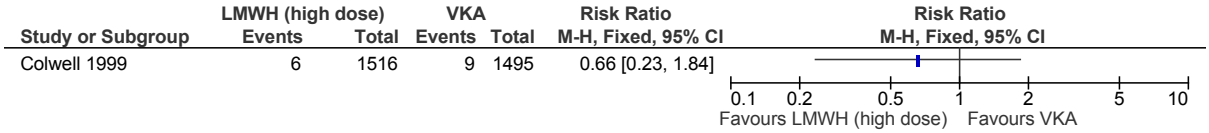
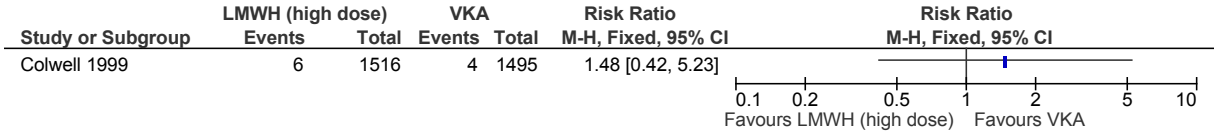


Figure 356: Major bleeding (time-point not reported)



L.23.26 LMWH (high dose; extended duration) versus VKA

Figure 357: All-cause mortality (42-63 days)

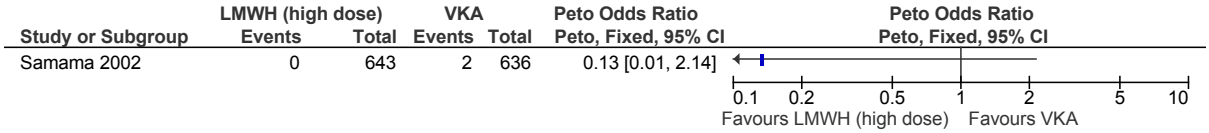


Figure 358: DVT (symptomatic and asymptomatic) (42-63 days)

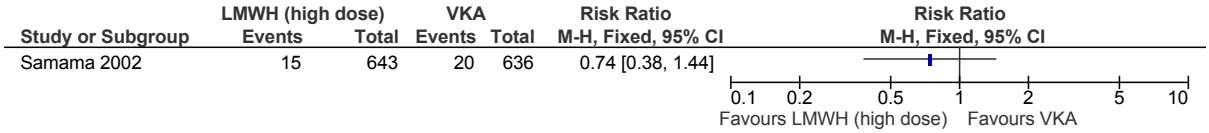


Figure 359: PE (42-63 days)

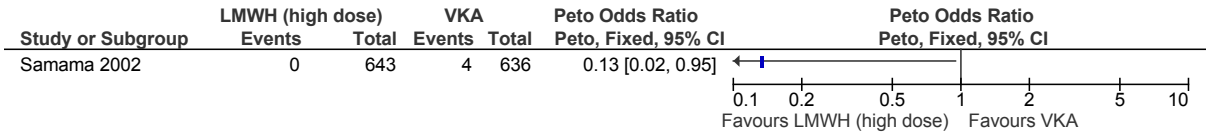
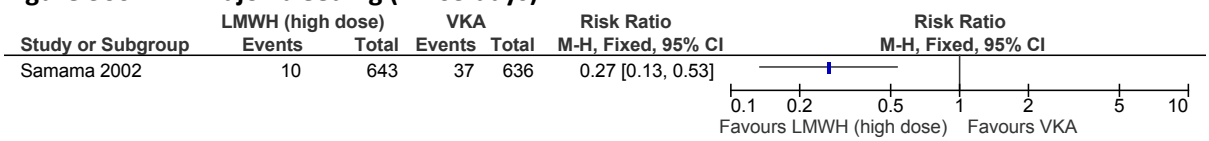


Figure 360: Major bleeding (42-63 days)



L.23.27 LMWH (low dose; pre-operation) versus VKA

Figure 361: All-cause mortality (8 days)

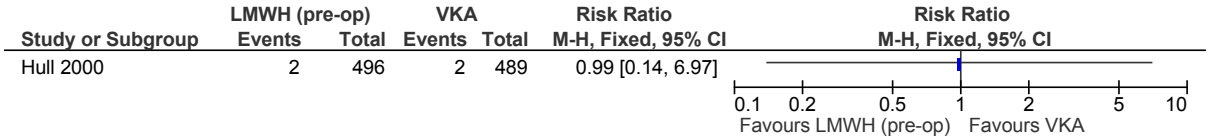


Figure 362: DVT (symptomatic and asymptomatic) (8 days)

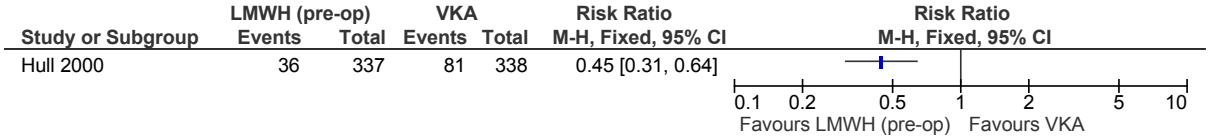


Figure 363: PE (8 days)

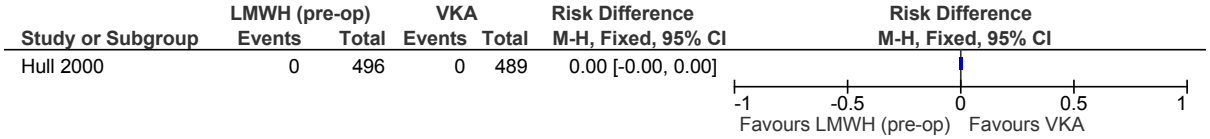


Figure 364: Major bleeding (8 days)

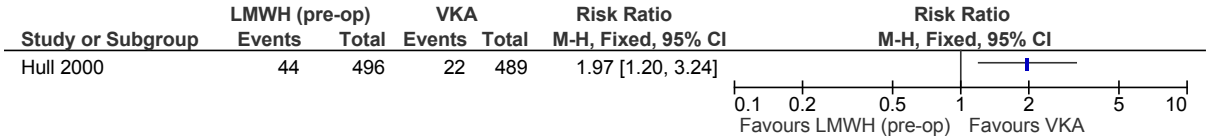
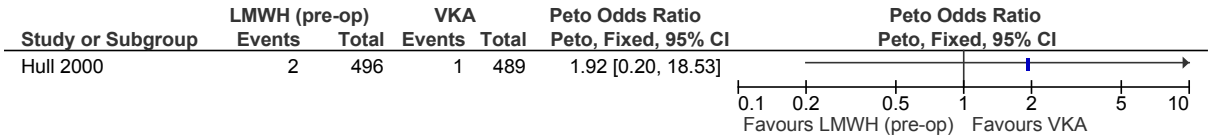


Figure 365: Wound haematomas (8 days)



L.23.28 LMWH (low dose; post-operation) versus VKA

Figure 366: All-cause mortality (8 days)

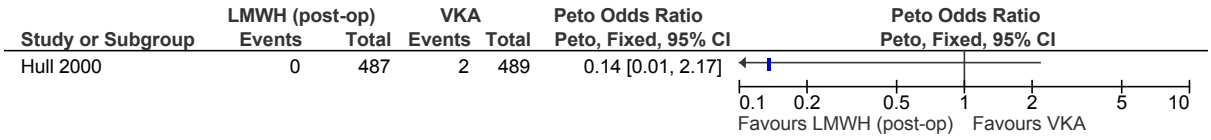


Figure 367: DVT (symptomatic and asymptomatic) (8 days)

Study or Subgroup	LMWH (post-op) Events	Total	VKA Events	Total	Risk Ratio M-H, Fixed, 95% CI
Hull 2000	44	336	81	338	0.55 [0.39, 0.76]

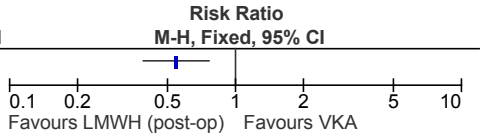


Figure 368: PE (8 days)

Study or Subgroup	LMWH (post-op) Events	Total	VKA Events	Total	Risk Difference M-H, Fixed, 95% CI
Hull 2000	0	487	0	489	0.00 [-0.00, 0.00]

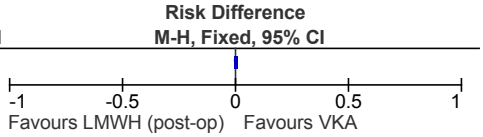


Figure 369: Major bleeding (8 days)

Study or Subgroup	LMWH (post-op) Events	Total	VKA Events	Total	Risk Ratio M-H, Fixed, 95% CI
Hull 2000	32	487	22	489	1.46 [0.86, 2.48]

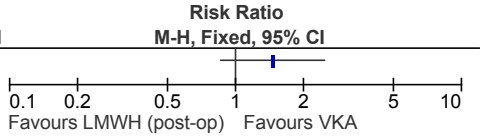
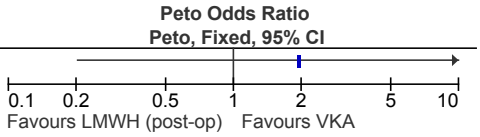


Figure 370: Wound haematomas (8 days)

Study or Subgroup	LMWH (post-op) Events	Total	VKA Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Hull 2000	2	487	1	489	1.96 [0.20, 18.87]



L.23.29 LMWH (low dose; pre-operation) versus LMWH (low dose; post-operation)

Figure 371: All-cause mortality (8 days)

Study or Subgroup	LMWH (pre-op) Events	Total	LMWH (post-op) Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Hull 2000	2	496	0	487	7.27 [0.45, 116.42]

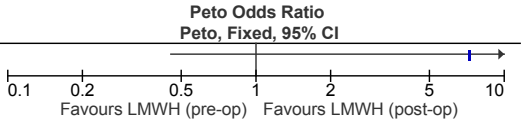


Figure 372: DVT (symptomatic and asymptomatic) (8 days)

Study or Subgroup	LMWH (pre-op) Events	Total	LMWH (post-op) Events	Total	Risk Ratio M-H, Fixed, 95% CI
Hull 2000	36	337	44	336	0.82 [0.54, 1.23]

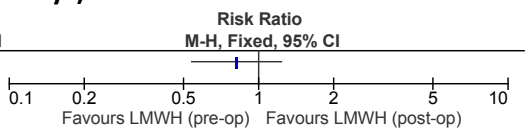


Figure 373: PE (8 days)

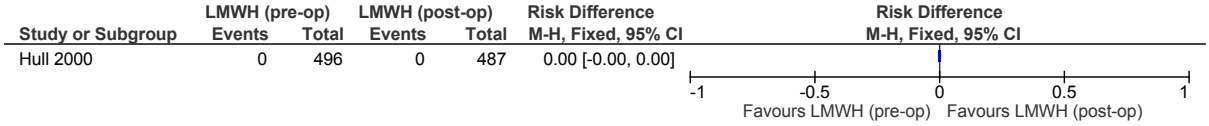


Figure 374: Major bleeding (8 days)

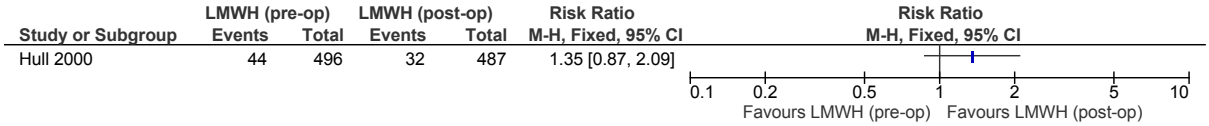
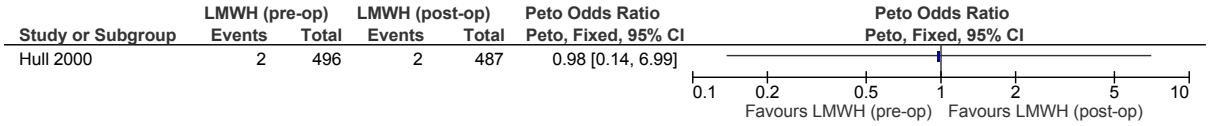
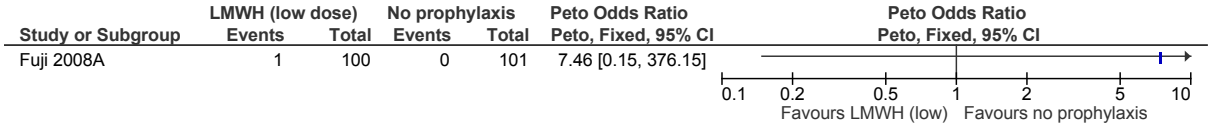


Figure 375: Wound haematoma (8 days)



L.23.30 LMWH (low dose; standard duration) versus no pharmacological prophylaxis

Figure 376: Major bleeding (15 days)



L.23.31 LMWH (low dose; standard duration) + AES versus AES (above-knee)

Figure 377: DVT (symptomatic and asymptomatic) (8-10 days)

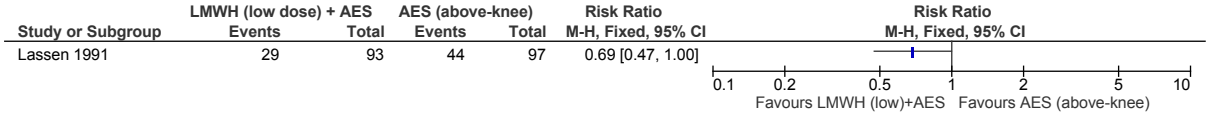


Figure 378: PE (8-10 days)

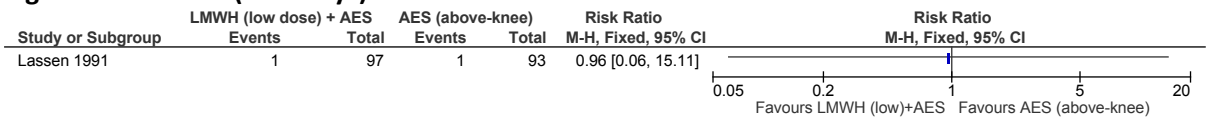
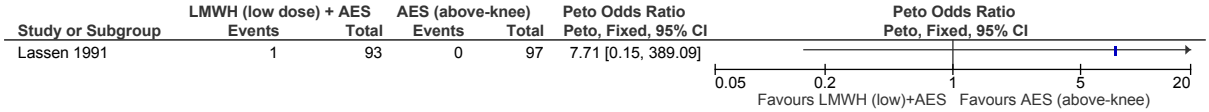


Figure 379: Fatal PE (8-10 days)



L.23.32 LMWH (low dose; standard duration) + AES versus AES (length unspecified)

Figure 380: DVT (symptomatic and asymptomatic) (14 days)

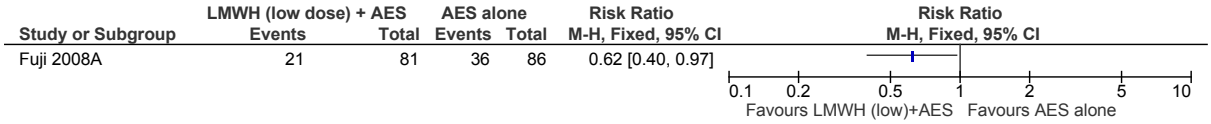
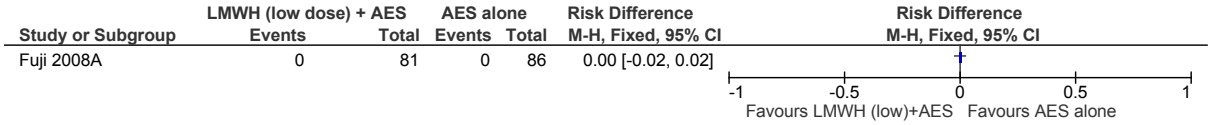
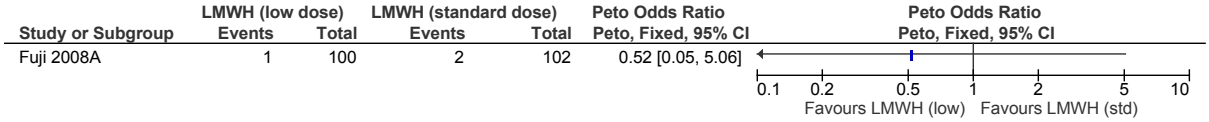


Figure 381: PE (90 days)



L.23.33 LMWH (low dose; standard duration) versus LMWH (standard dose; standard duration)

Figure 382: Major bleeding (15 days)



L.23.34 LMWH (low dose; standard duration) + AES versus LMWH (standard dose; standard duration) + AES

Figure 383: DVT (symptomatic and asymptomatic) (14 days)

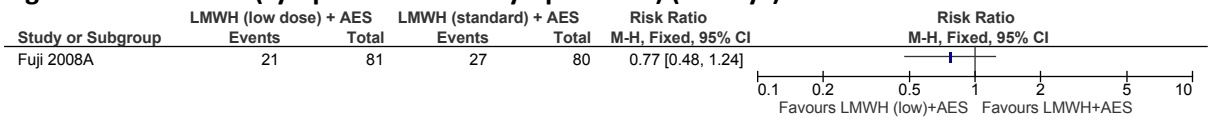
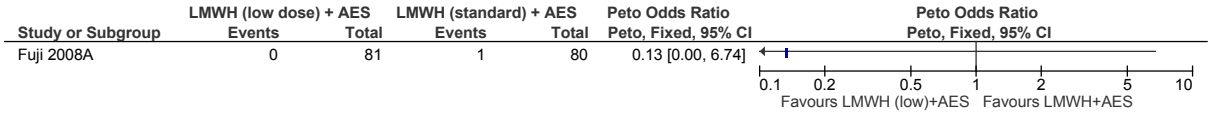
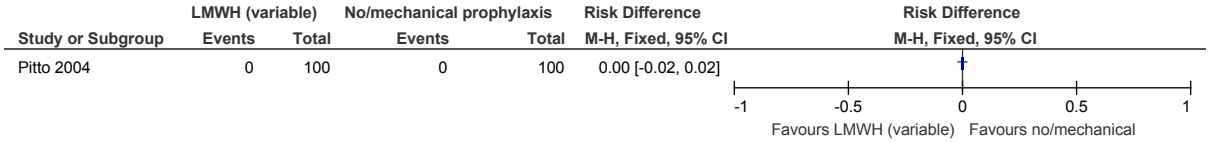


Figure 384: PE (90 days)



L.23.35 LMWH (variable dose; standard duration) versus no prophylaxis

Figure 385: Major bleeding (45 days)



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

L.23.36 LMWH (variable dose; standard duration) + AES versus foot pump + AES

Figure 386: DVT (symptomatic and asymptomatic) (45 days)

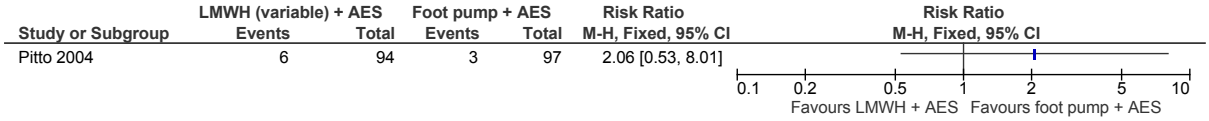


Figure 387: PE (45 days)

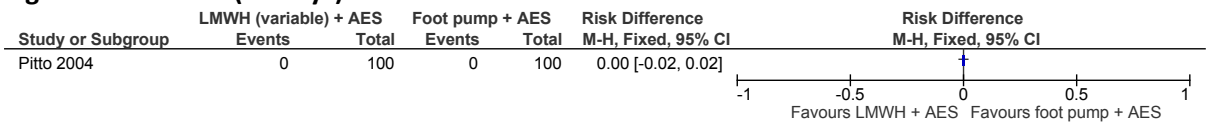


Figure 388: Fatal PE (45 days)

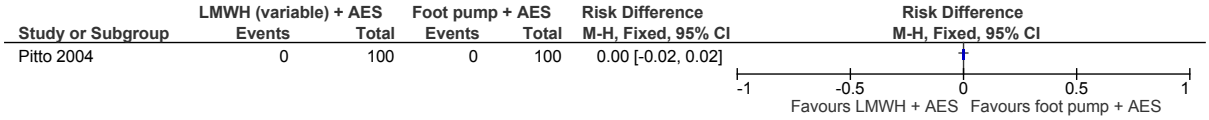
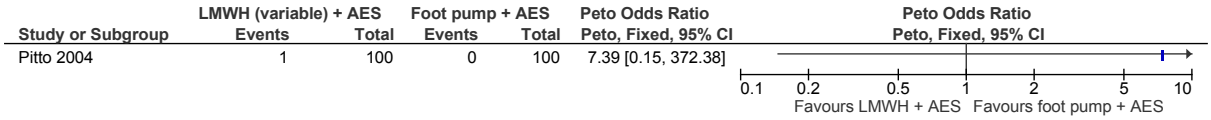


Figure 389: Heparin-induced thrombocytopenia (45 days)



L.23.37 UFH versus no prophylaxis

Figure 390: DVT (symptomatic and asymptomatic) (time-point not reported)

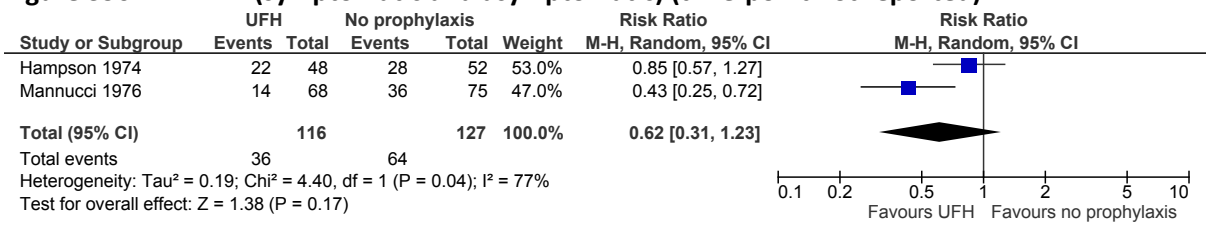


Figure 391: Major bleeding (time-point not reported)

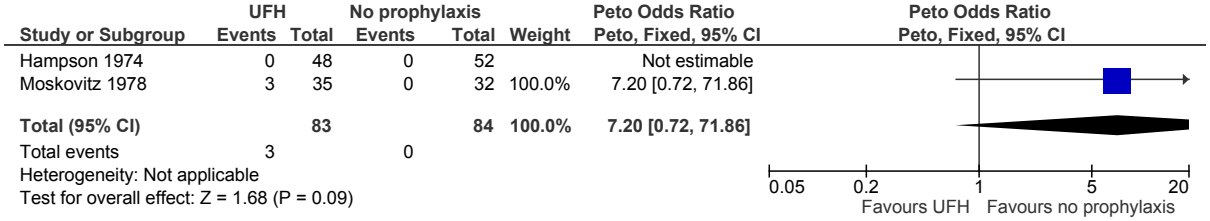
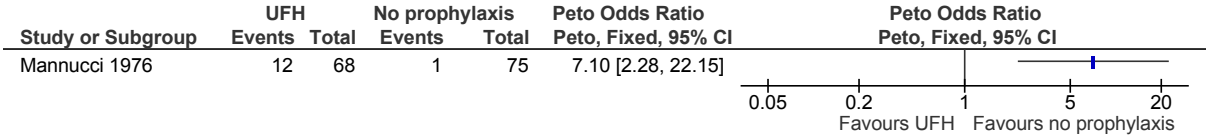


Figure 392: Wound haematoma (time-point not reported)



L.23.38 UFH (extended duration) versus UFH (standard duration)

Figure 393: DVT (symptomatic and asymptomatic) (45 days)

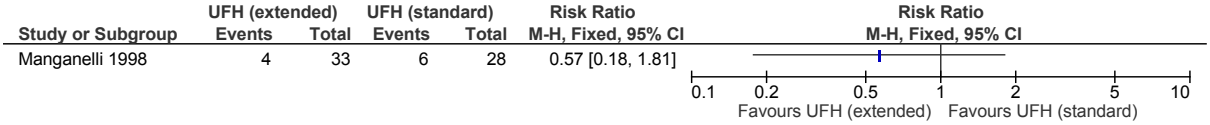
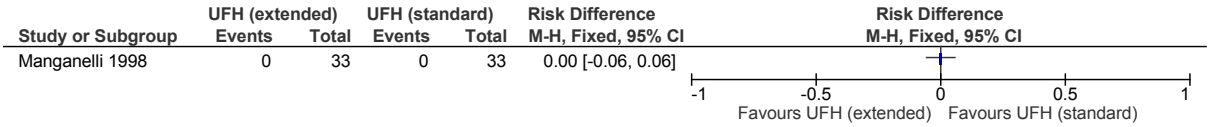


Figure 394: Major bleeding (45 days)



L.23.39 UFH versus aspirin

Figure 395: DVT (symptomatic and asymptomatic) (7 days)

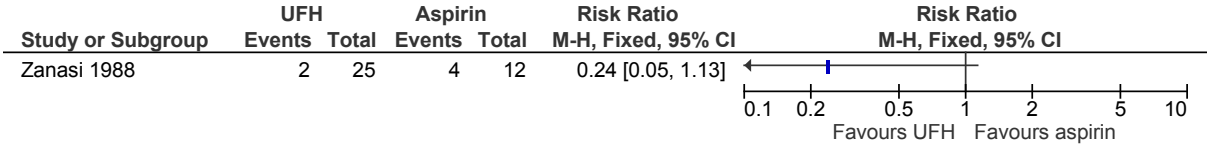


Figure 396: PE (7 days)

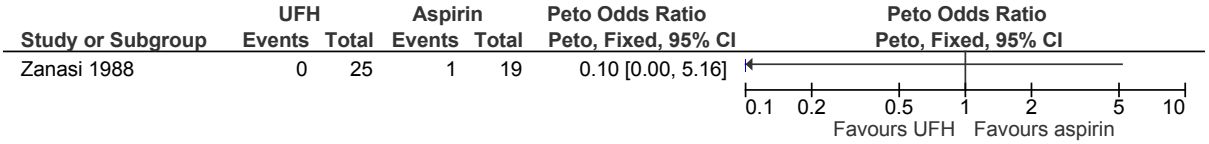
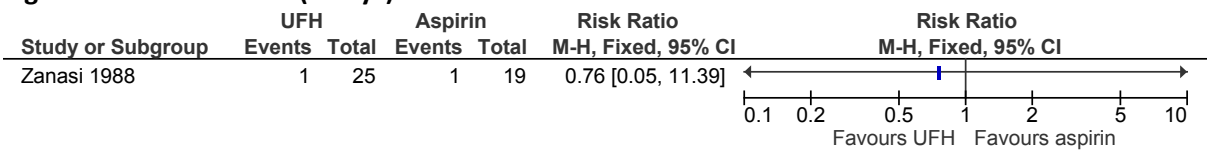


Figure 397: Fatal PE (7 days)



L.23.40 UFH + AES (length unspecified) versus AES (length unspecified)

Figure 398: All-cause mortality (time-point not reported)

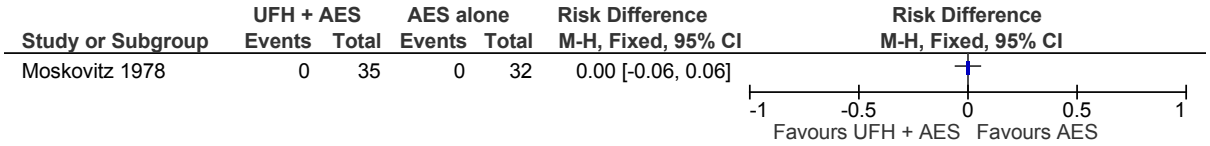


Figure 399: DVT (symptomatic and asymptomatic) (10 days)

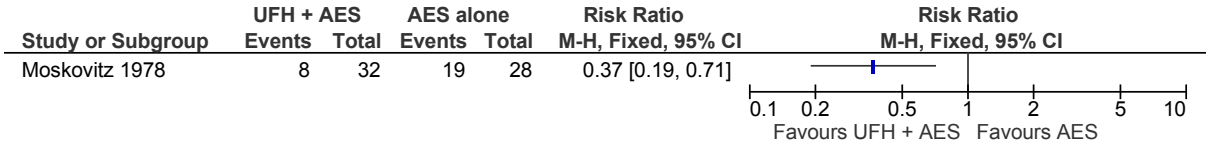
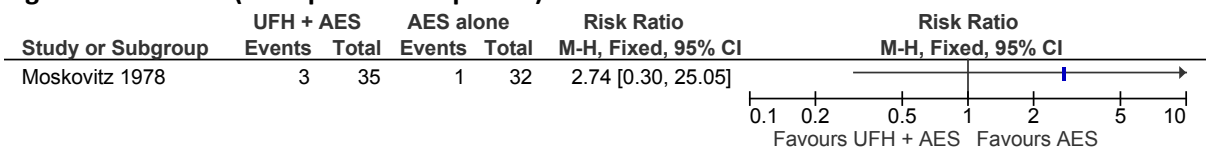
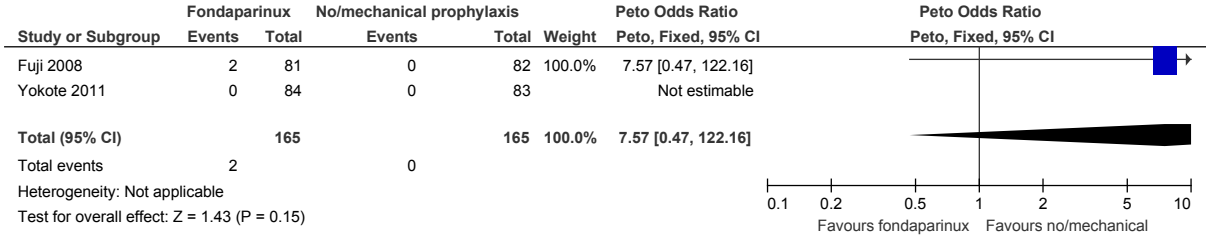


Figure 400: PE (time-point not reported)



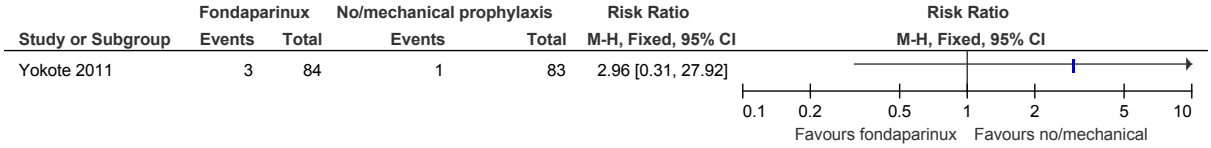
L.23.41 Fondaparinux versus no prophylaxis

Figure 401: **Major bleeding (11-17 days)**



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

Figure 402: **Wound haematoma (11 days)**

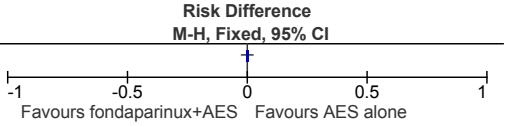


No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

L.23.42 Fondaparinux + AES versus AES alone

Figure 403: All-cause mortality (17 days)

Study or Subgroup	Fondaparinux + AES Events	Total	AES alone Events	Total	Risk Difference M-H, Fixed, 95% CI
Fuji 2008	0	81	0	82	0.00 [-0.02, 0.02]



L.23.43 Fondaparinux + IPCD + AES versus IPCD + AES

Figure 404: DVT (symptomatic and asymptomatic) (11 days)

Study or Subgroup	Fondaparinux + IPCD + AES Events	Total	IPCD + GCS Events	Total	Risk Ratio M-H, Fixed, 95% CI
Yokote 2011	6	84	6	83	0.99 [0.33, 2.94]

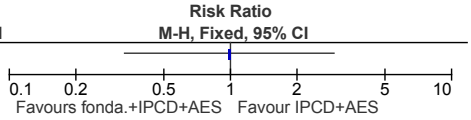
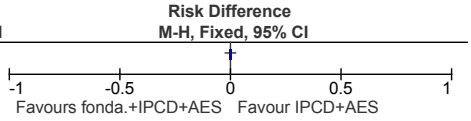


Figure 405: PE (11 days)

Study or Subgroup	Fondaparinux + IPCD + AES Events	Total	IPCD + GCS Events	Total	Risk Difference M-H, Fixed, 95% CI
Yokote 2011	0	84	0	83	0.00 [-0.02, 0.02]



L.23.44 Fondaparinux + AES versus fondaparinux

Figure 406: All-cause mortality (35-49 days)

Study or Subgroup	Fondaparinux + AES Events	Total	Fondaparinux Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Cohen 2007	1	391	3	404	0.38 [0.05, 2.70]

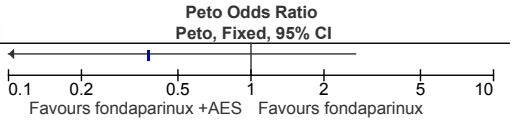


Figure 407: Major bleeding (35-49 days)

Study or Subgroup	Fondaparinux + AES Events	Total	Fondaparinux Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Cohen 2007	0	391	1	404	0.14 [0.00, 7.05]

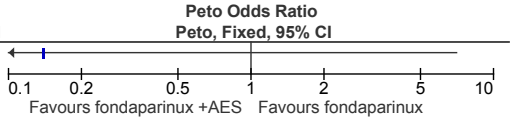


Figure 408: Fatal PE (35-49 days)

Study or Subgroup	Fondaparinux + AES Events	Total	Fondaparinux Events	Total	Risk Difference M-H, Fixed, 95% CI
Cohen 2007	0	391	0	404	0.00 [-0.00, 0.00]

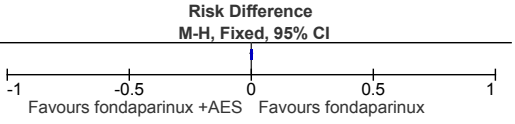
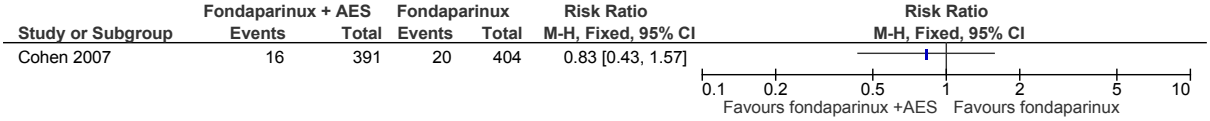


Figure 409: Clinically relevant non-major bleeding (35-49 days)



L.23.45 Fondaparinux + IPCD versus VKA + IPCD

Figure 410: All-cause mortality (30 days)

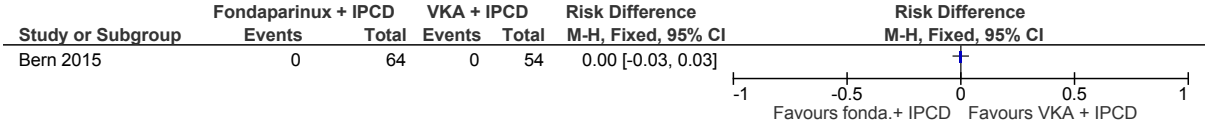


Figure 411: DVT (symptomatic and asymptomatic) (30 days)

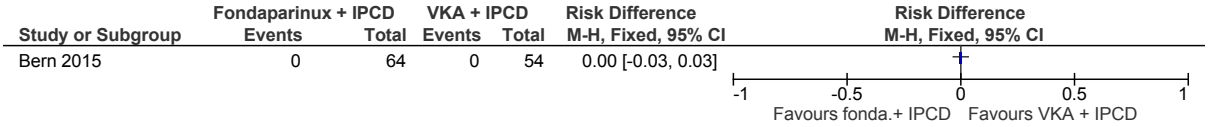
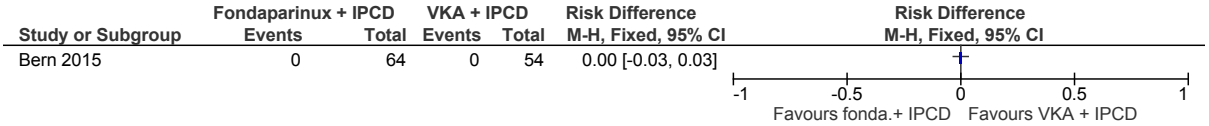


Figure 412: PE (30 days)



L.23.46 IPCD versus no prophylaxis

Figure 413: DVT (symptomatic and asymptomatic) (time-point not reported)

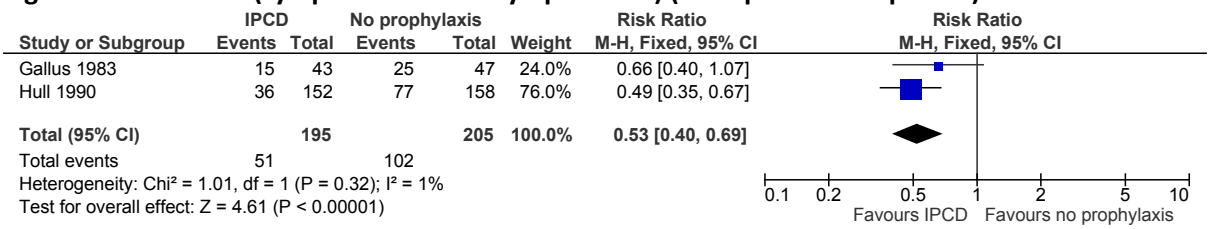
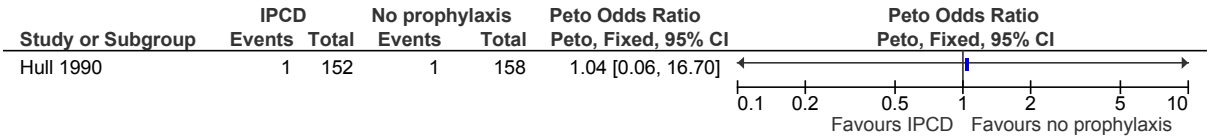
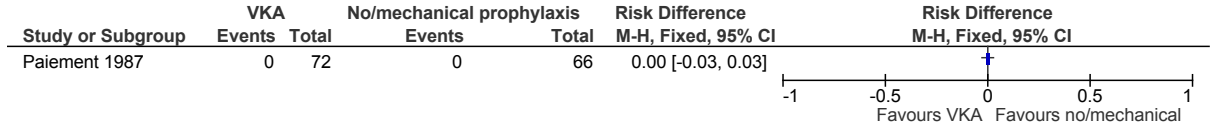


Figure 414: PE (time-point not reported)



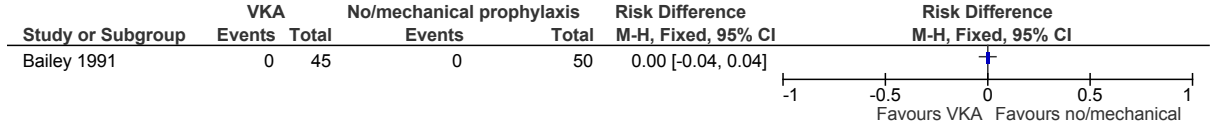
L.23.47 VKA versus no prophylaxis

Figure 415: **Major bleeding (10 days)**



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

Figure 416: **Clinically relevant non-major bleeding (7 days)**



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

L.23.48 VKA (extended duration) versus VKA (standard duration)

Figure 417: All-cause mortality (28 days)

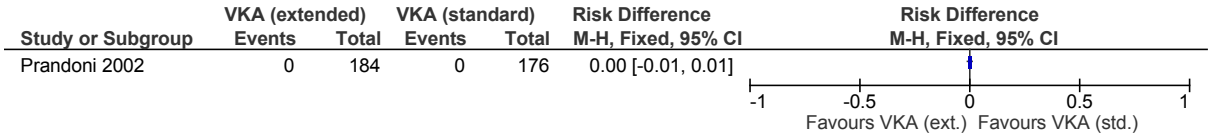


Figure 418: DVT (symptomatic and asymptomatic) (28 days)

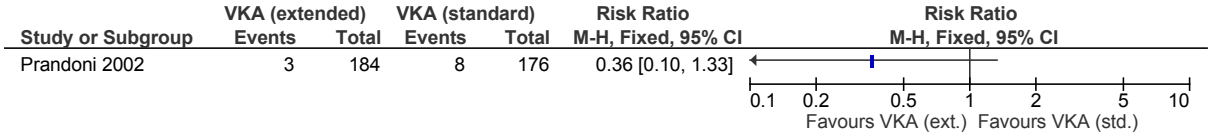


Figure 419: PE (28 days)

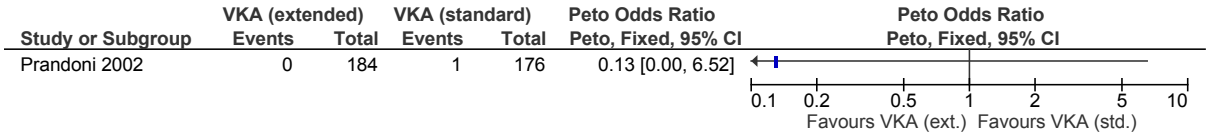
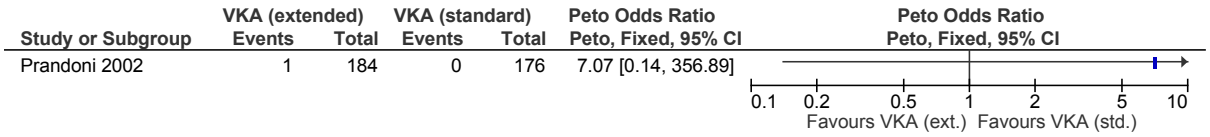


Figure 420: Major bleeding (28 days)



L.23.49 IPCD versus VKA

Figure 421: DVT (symptomatic and asymptomatic (10 days)

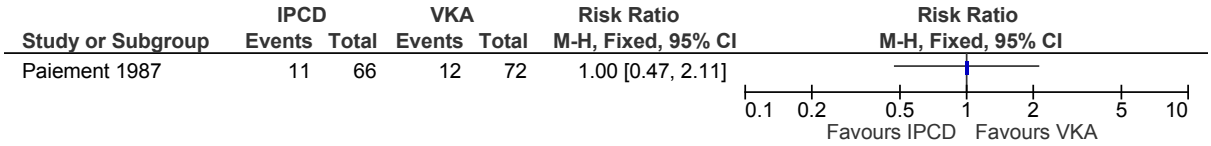
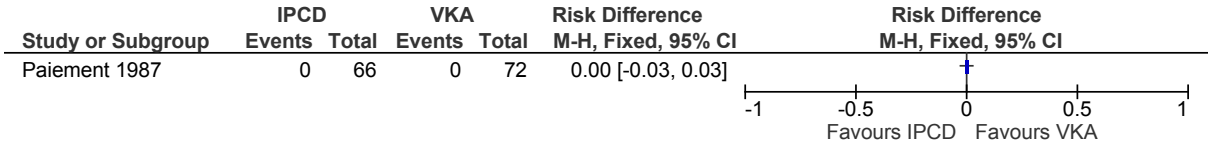
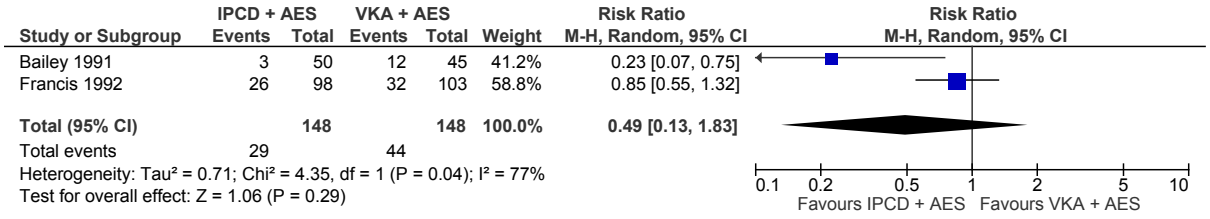


Figure 422: PE (10 days)



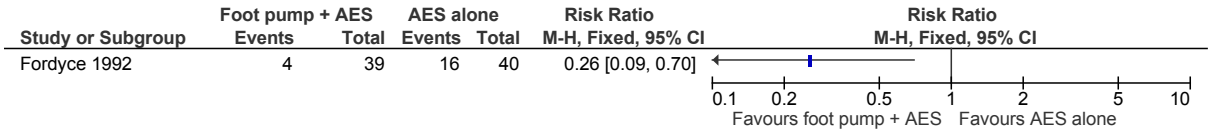
L.23.50 IPCD + AES versus VKA + AES

Figure 423: DVT (symptomatic and asymptomatic) (8 days)



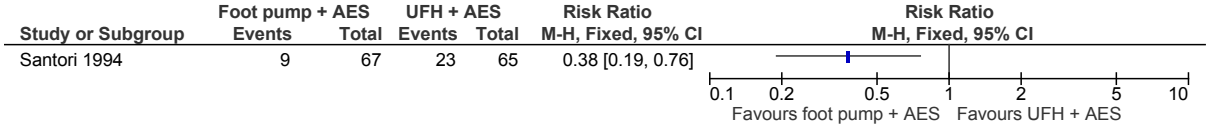
L.23.51 Foot pump + AES versus AES alone

Figure 424: DVT (symptomatic and asymptomatic) (6-9 days)



L.23.52 Foot pump + AES versus UFH + AES

Figure 425: DVT (symptomatic and asymptomatic) (42 days)



L.24 Elective knee replacement

L.24.1 LMWH (standard dose; standard duration) versus no prophylaxis

Figure 426: DVT (symptomatic and asymptomatic) (30 days)

Study or Subgroup	LMWH (standard dose) Events	Total	No prophylaxis Events	Total	Risk Ratio M-H, Fixed, 95% CI
Chin 2009	6	110	24	110	0.25 [0.11, 0.59]

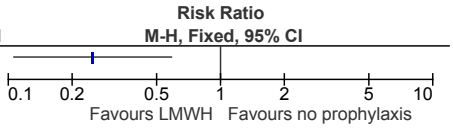


Figure 427: PE (30 days)

Study or Subgroup	LMWH (standard dose) Events	Total	No prophylaxis Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Chin 2009	0	110	1	110	0.14 [0.00, 6.82]

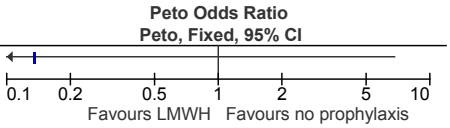
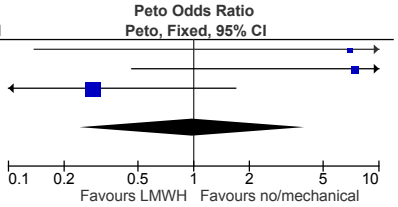


Figure 428: Major bleeding (15 days)

Study or Subgroup	LMWH (standard dose) Events	Total	No/mechanical prophylaxis Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Blanchard 1999A	1	67	0	63	12.7%	6.96 [0.14, 351.46]
Chin 2009	2	110	0	110	25.3%	7.46 [0.46, 119.98]
Fuji 2008A	1	91	4	89	62.0%	0.29 [0.05, 1.69]
Total (95% CI)		**268**		**262**	**100.0%**	**0.98 [0.24, 3.95]**
Total events	4		4			

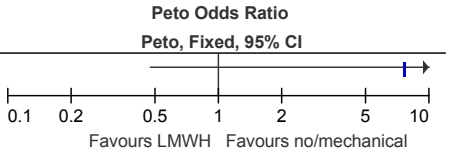
Heterogeneity: Chi² = 4.86, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 0.03 (P = 0.98)



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

Figure 429: **Wound haematoma (time point not reported)**

Study or Subgroup	LMWH Events	Total	No/mechanical prophylaxis Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Warwick 2002	2	108	0	111	7.67 [0.48, 123.42]



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

Figure 430: Technical complications of mechanical interventions (time-point not reported)

Study or Subgroup	LMWH (standard dose) Events	Total	No prophylaxis Events	Total	Risk Difference M-H, Fixed, 95% CI
Chin 2009	0	110	0	110	0.00 [-0.02, 0.02]

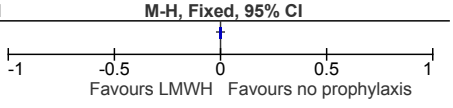
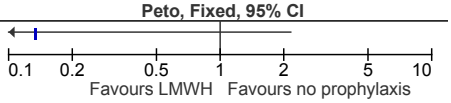


Figure 431: Wound infection (30 days)

Study or Subgroup	LMWH (standard dose) Events	Total	No prophylaxis Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Chin 2009	0	110	2	110	0.13 [0.01, 2.16]



L.24.2 LMWH (standard dose; standard duration) versus apixaban

Figure 432: All-cause mortality (60 days)

Study or Subgroup	LMWH Events	Total	Apixaban Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Lassen 2010	1	1529	3	1528	0.37 [0.05, 2.61]

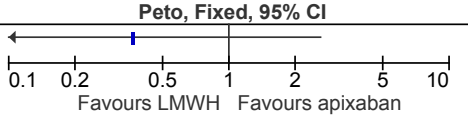


Figure 433: DVT (symptomatic and asymptomatic) (14 days)

Study or Subgroup	LMWH Events	Total	Apixaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lassen 2010	243	997	142	971	1.67 [1.38, 2.01]

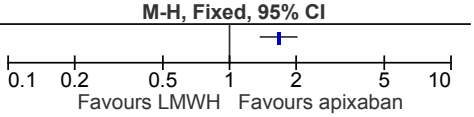


Figure 434: PE (14 days)

Study or Subgroup	LMWH Events	Total	Apixaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lassen 2010	1	1529	6	1528	0.17 [0.02, 1.38]

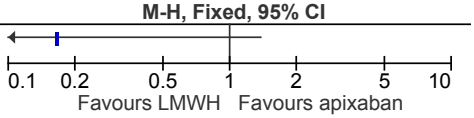


Figure 435: Major bleeding (14 days)

Study or Subgroup	LMWH Events	Total	Apixaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lassen 2010	14	1508	9	1501	1.55 [0.67, 3.57]

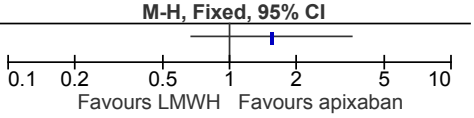


Figure 436: Fatal PE (14 days)

Study or Subgroup	LMWH Events	Total	Apixaban Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Lassen 2010	0	1529	1	1528	0.14 [0.00, 6.82]

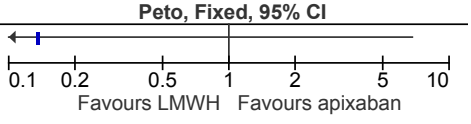


Figure 437: Clinically relevant non-major bleeding (14 days)

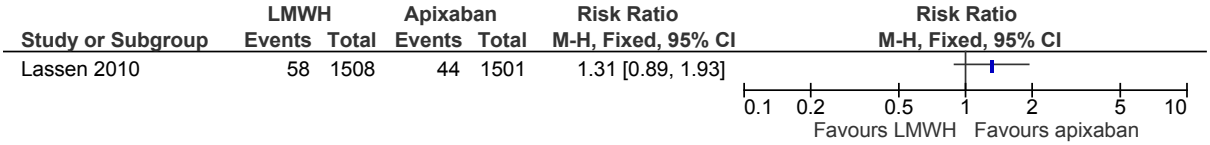
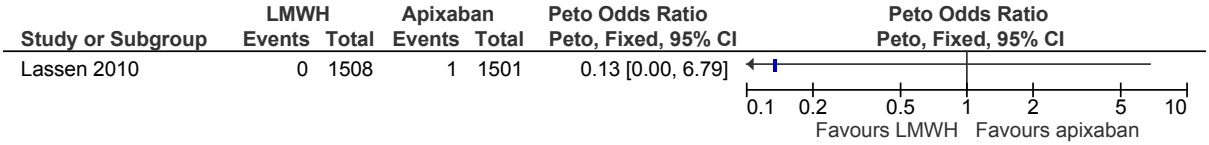


Figure 438: Wound haematoma (14 days)



L.24.3 LMWH (standard dose; standard duration) versus dabigatran

Figure 439: All-cause mortality (13 days)

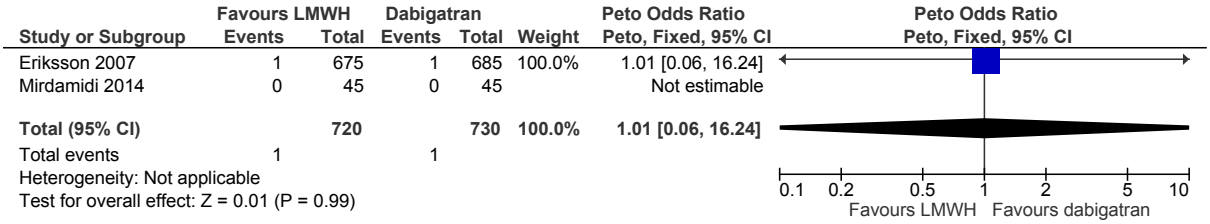


Figure 440: DVT (symptomatic and asymptomatic) (13 days)

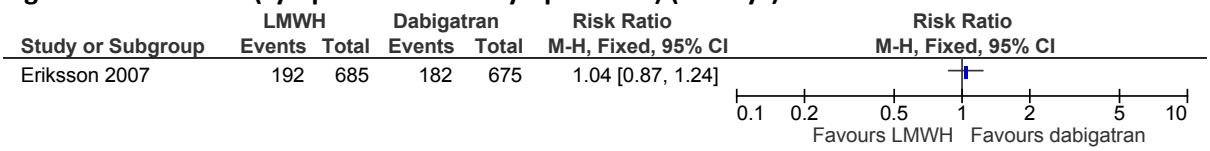


Figure 441: PE (13 days)

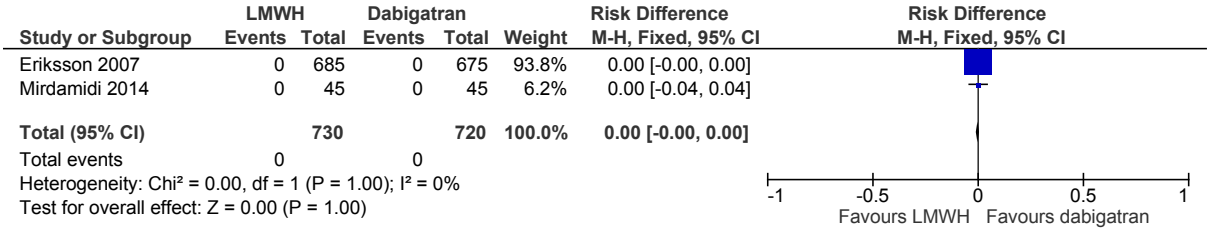


Figure 442: Major bleeding (13 days)

Study or Subgroup	LMWH Events	LMWH Total	Dabigatran Events	Dabigatran Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eriksson 2007	9	694	10	679	77.1%	0.88 [0.36, 2.15]
Mirdamidi 2014	2	45	3	45	22.9%	0.67 [0.12, 3.80]
Total (95% CI)		**739**		**724**	**100.0%**	**0.83 [0.38, 1.84]**
Total events	11		13			

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)

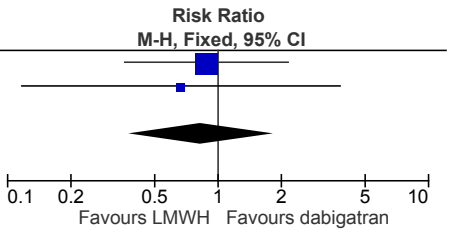


Figure 443: Fatal PE (13 days)

Study or Subgroup	LMWH Events	LMWH Total	Dabigatran Events	Dabigatran Total	Peto Odds Ratio Peto, Fixed, 95% CI
Eriksson 2007	1	685	0	675	7.28 [0.14, 367.03]

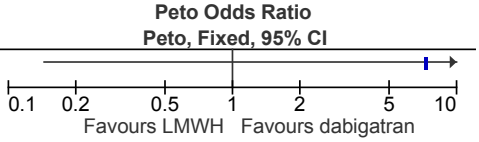
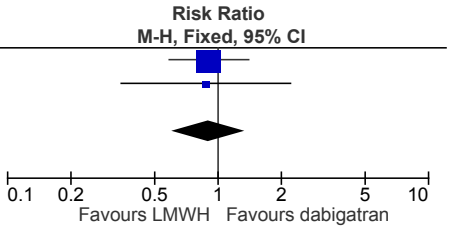


Figure 444: Clinically relevant non-major bleeding (13 days)

Study or Subgroup	LMWH Events	LMWH Total	Dabigatran Events	Dabigatran Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eriksson 2007	37	694	40	679	83.5%	0.91 [0.59, 1.40]
Mirdamidi 2014	7	45	8	45	16.5%	0.88 [0.35, 2.21]
Total (95% CI)		**739**		**724**	**100.0%**	**0.90 [0.61, 1.33]**
Total events	44		48			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.60)



L.24.4 LMWH (standard dose; standard duration) versus rivaroxaban

Figure 445: All-cause mortality (35 days)

Study or Subgroup	LMWH Events	LMWH Total	Rivaroxaban Events	Rivaroxaban Total	Peto Odds Ratio Peto, Fixed, 95% CI
Lassen 2008	4	1217	0	1201	7.31 [1.03, 51.96]

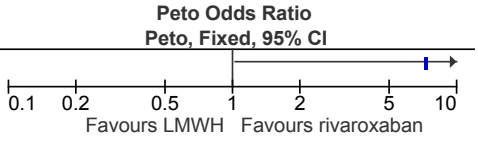


Figure 446: DVT (symptomatic and asymptomatic) (28 days)

Study or Subgroup	LMWH Events	LMWH Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lassen 2008	160	878	79	824	96.3%	1.90 [1.48, 2.45]
Zou 2014	14	112	3	102	3.7%	4.25 [1.26, 14.36]
Total (95% CI)		**990**		**926**	**100.0%**	**1.99 [1.55, 2.54]**
Total events	174		82			

Heterogeneity: Chi² = 1.62, df = 1 (P = 0.20); I² = 38%
Test for overall effect: Z = 5.46 (P < 0.00001)

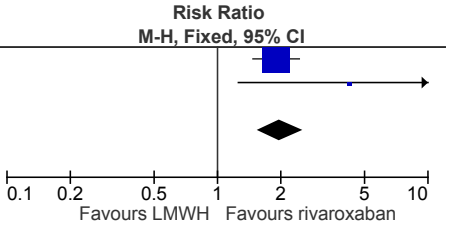


Figure 447: PE (17 days)

Study or Subgroup	LMWH Events	LMWH Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Lassen 2008	4	1217	0	1201	100.0%	7.31 [1.03, 51.96]
Zou 2014	0	112	0	102		Not estimable
Total (95% CI)		**1329**		**1303**	**100.0%**	**7.31 [1.03, 51.96]**
Total events	4		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)

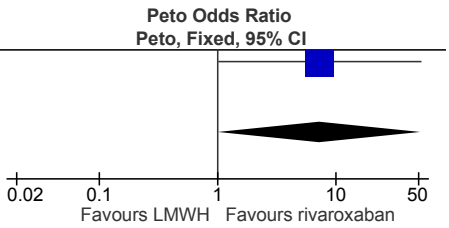


Figure 448: Major bleeding (17 days)

Study or Subgroup	LMWH Events	LMWH Total	Rivaroxaban Events	Rivaroxaban Total	Risk Ratio M-H, Fixed, 95% CI
Lassen 2008	17	1277	21	1254	0.79 [0.42, 1.50]

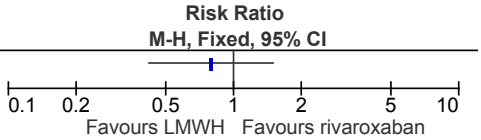


Figure 449: Clinically relevant non-major bleeding (35 days)

Study or Subgroup	LMWH Events	LMWH Total	Rivaroxaban Events	Rivaroxaban Total	Risk Ratio M-H, Fixed, 95% CI
Lassen 2008	28	1239	33	1220	0.84 [0.51, 1.37]

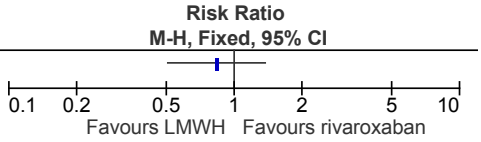
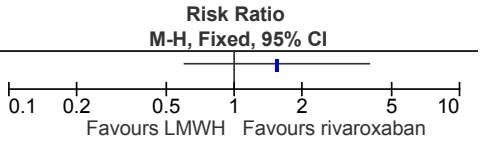


Figure 450: Wound infection (17 days)

Study or Subgroup	LMWH Events	LMWH Total	Rivaroxaban Events	Rivaroxaban Total	Risk Ratio M-H, Fixed, 95% CI
Lassen 2008	11	1239	7	1220	1.55 [0.60, 3.98]



L.24.5 LMWH (standard dose; standard duration) versus aspirin

Figure 451: DVT (symptomatic and asymptomatic (28 days)

Study or Subgroup	LMWH Events	LMWH Total	Aspirin Events	Aspirin Total	Risk Ratio M-H, Fixed, 95% CI
Zou 2014	14	112	18	110	0.76 [0.40, 1.46]

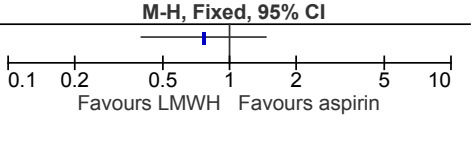
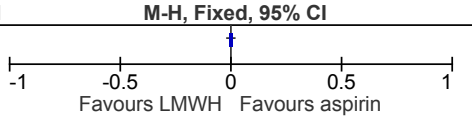


Figure 452: PE (28 days)

Study or Subgroup	LMWH Events	LMWH Total	Aspirin Events	Aspirin Total	Risk Difference M-H, Fixed, 95% CI
Zou 2014	0	112	0	110	0.00 [-0.02, 0.02]



L.24.6 LMWH (standard dose; standard duration) versus AES

Figure 453: DVT (symptomatic and asymptomatic (30 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Risk Ratio M-H, Fixed, 95% CI
Chin 2009	6	110	14	110	0.43 [0.17, 1.07]

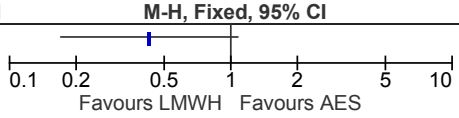


Figure 454: PE (30 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Peto Odds Ratio Peto, Fixed, 95% CI
Chin 2009	0	110	1	110	0.14 [0.00, 6.82]

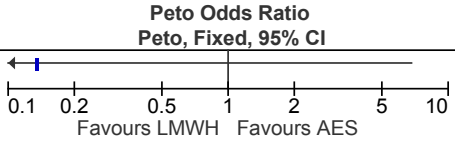


Figure 455: Technical complications of mechanical interventions (time-point not reported)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Risk Difference M-H, Fixed, 95% CI
Chin 2009	0	110	0	110	0.00 [-0.02, 0.02]

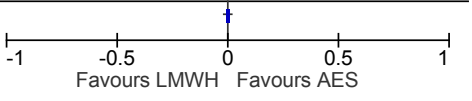
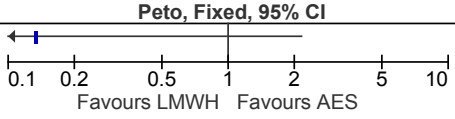


Figure 456: Wound infection (30 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Peto Odds Ratio Peto, Fixed, 95% CI
Chin 2009	0	110	2	110	0.13 [0.01, 2.16]



L.24.7 LMWH (standard dose; standard duration) versus IPCD

Figure 457: DVT (symptomatic and asymptomatic) (30 days)

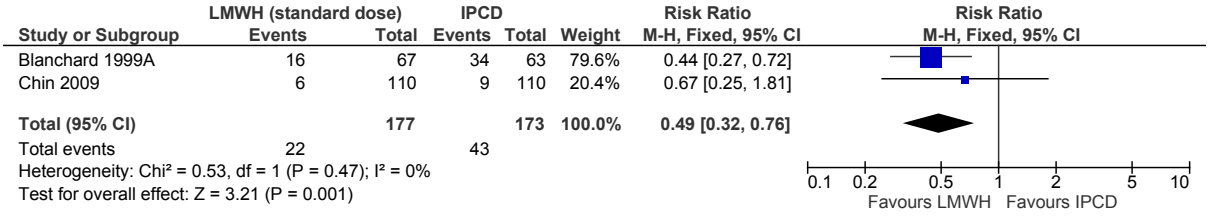


Figure 458: PE (30 days)

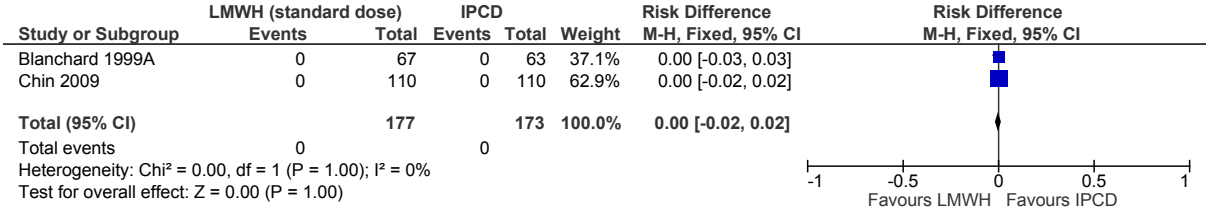


Figure 459: Technical complications of mechanical interventions (time-point not reported)

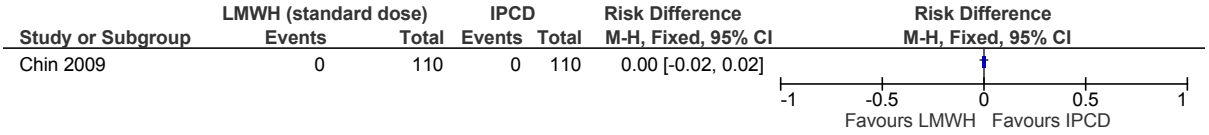
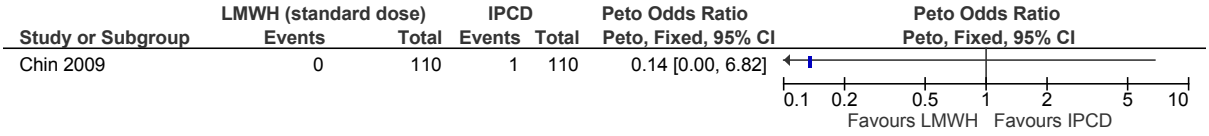


Figure 460: Wound infection (30 days)



L.24.8 LMWH (standard dose; standard duration) versus foot pump + AES

Figure 461: DVT (symptomatic and asymptomatic) (10 days)

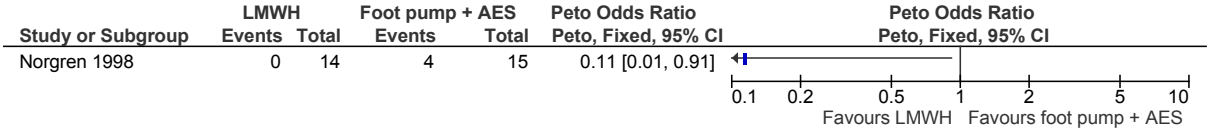
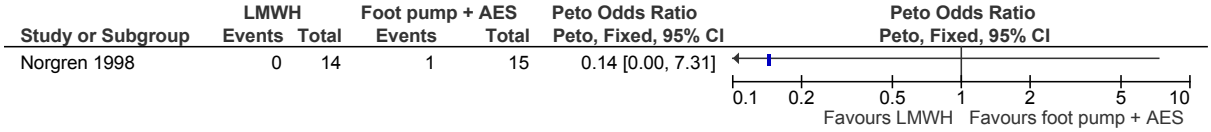


Figure 462: Fatal PE (time-point not reported)



L.24.9 LMWH (standard dose; standard duration) + AES versus foot pump + AES

Figure 463: DVT (symptomatic and asymptomatic) (8 days)

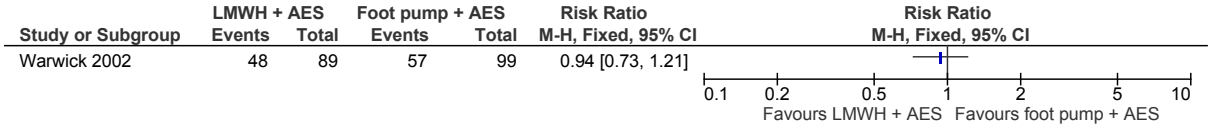
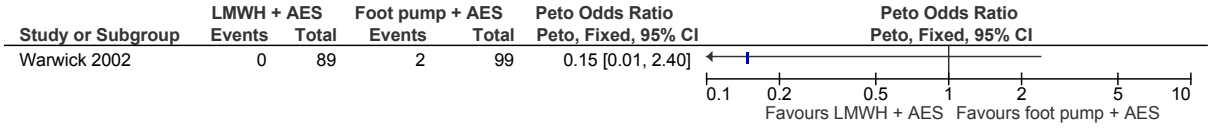
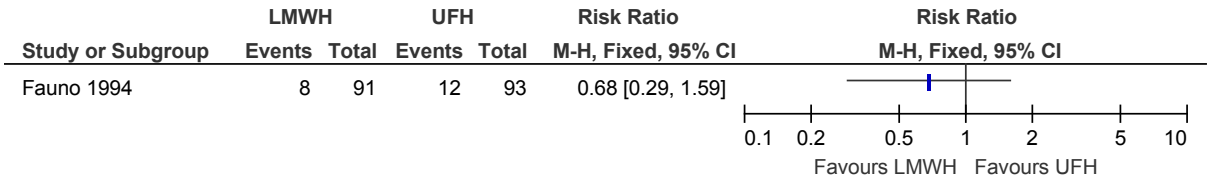


Figure 464: Fatal PE (8 days)



L.24.10 LMWH (standard dose; standard duration) versus UFH

Figure 465: **Wound haematoma (7-9 days)**



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

L.24.11 LMWH (standard dose; standard duration) + AES versus UFH + AES

Figure 466: DVT (symptomatic and asymptomatic) (7-9 days)

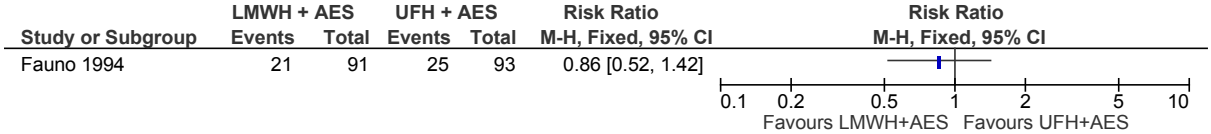


Figure 467: PE (7-9 days)

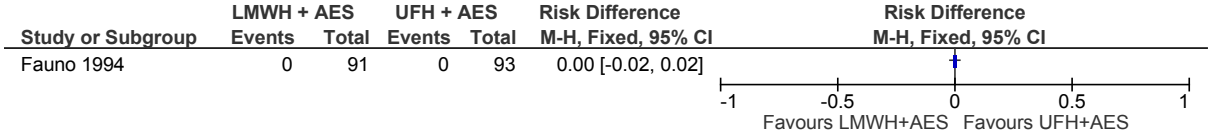
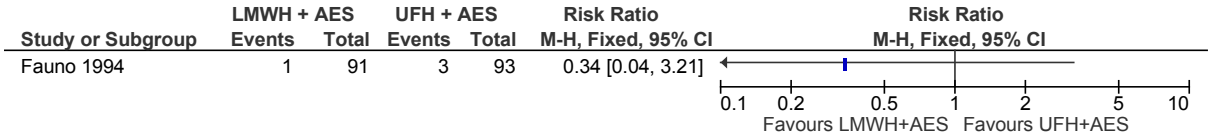


Figure 468: Wound infection (7-9 days)



L.24.12 LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)

Figure 469: DVT (symptomatic and asymptomatic) (27-29 days)

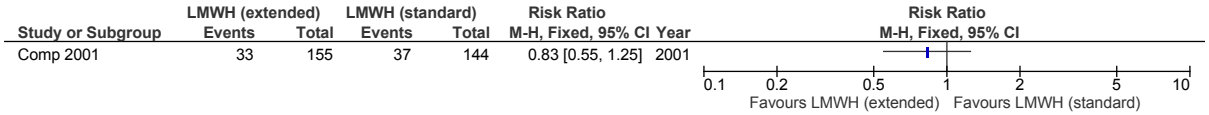


Figure 470: PE (27-29 days)

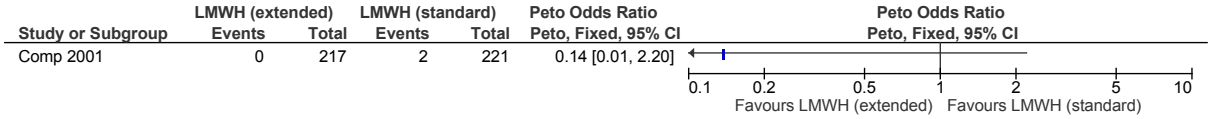


Figure 471: Major bleeding (27-29 days)

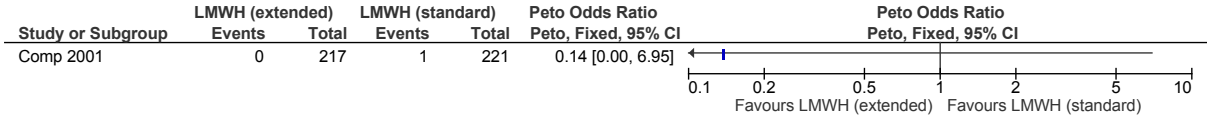
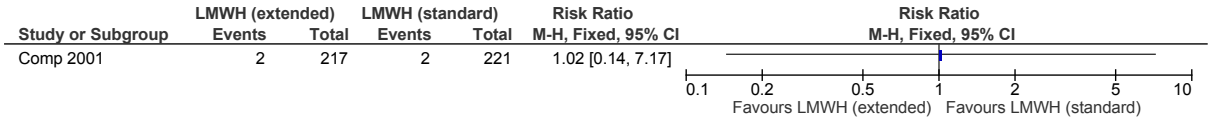


Figure 472: Heparin-induced thrombocytopenia (27-29 days)



L.24.13 LMWH (standard dose; standard duration) + AES versus LMWH (low dose; standard duration) + AES

Figure 473: DVT (symptomatic and asymptomatic) (14 days)

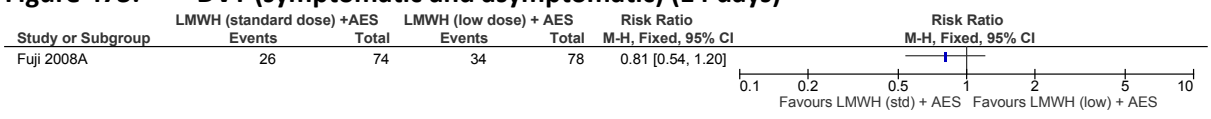
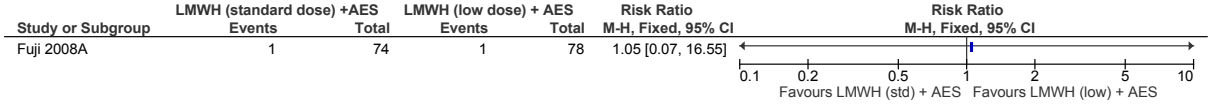


Figure 474: PE (90 days)



L.24.14 LMWH (standard dose; standard duration) + AES versus AES

Figure 475: DVT (symptomatic and asymptomatic) (14 days)

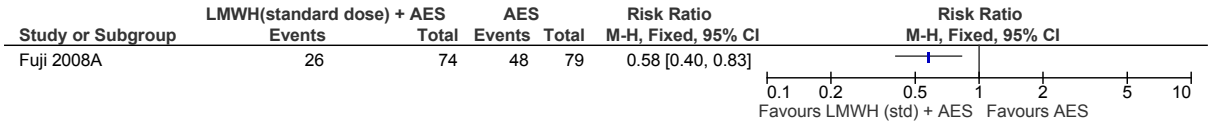
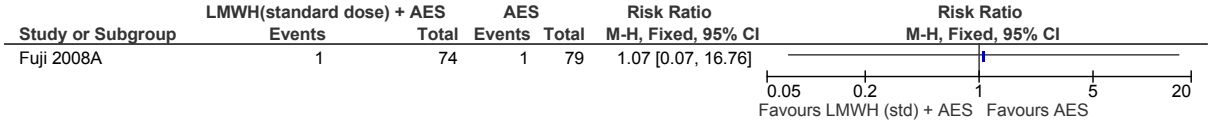
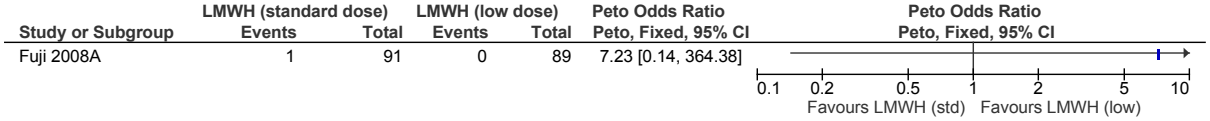


Figure 476: PE (90 days)



L.24.15 LMWH (standard dose; standard duration) versus LMWH (low dose; standard duration)

Figure 477: Major bleeding (15 days)



L.24.16 LMWH (standard dose; standard duration) + CPM versus CPM

Figure 478: DVT (symptomatic and asymptomatic) (6-10 days)

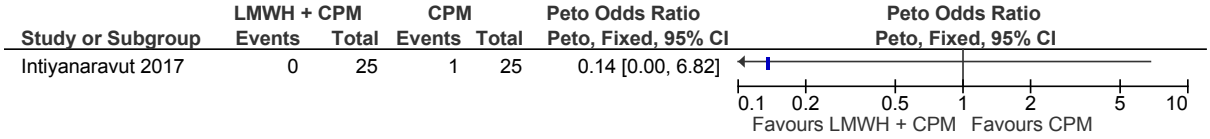


Figure 479: PE (time-point not reported)

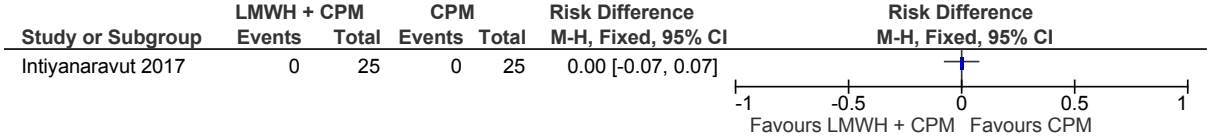
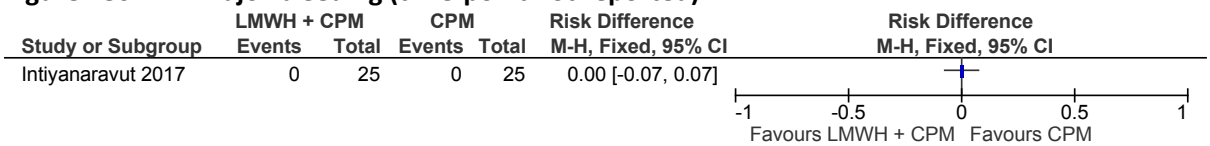
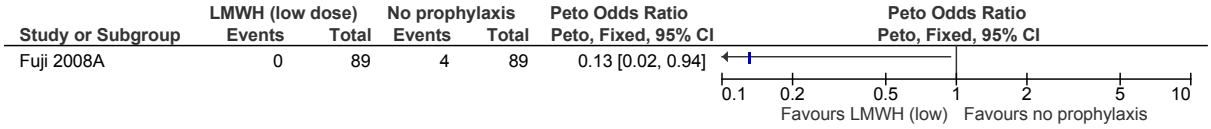


Figure 480: Major bleeding (time-point not reported)



L.24.17 LMWH (low dose; standard duration) versus no pharmacological prophylaxis

Figure 481: Major bleeding (15 days)



L.24.18 LMWH (low dose; standard duration) + AES versus AES

Figure 482: DVT (symptomatic and asymptomatic) (14 days)

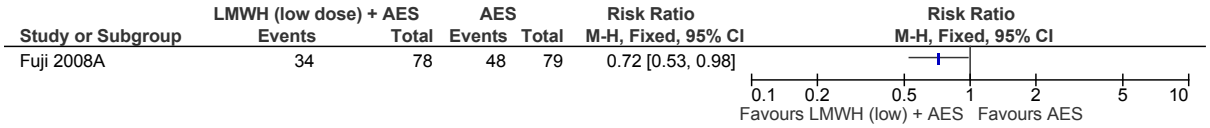
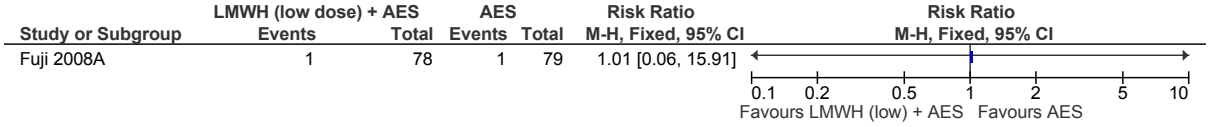


Figure 483: PE (90 days)



L.24.19 LMWH (high dose; standard duration) versus no prophylaxis

Figure 484: All-cause mortality (14 days)

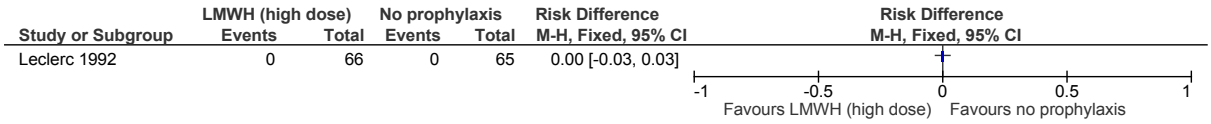


Figure 485: DVT (symptomatic and asymptomatic) (14 days)

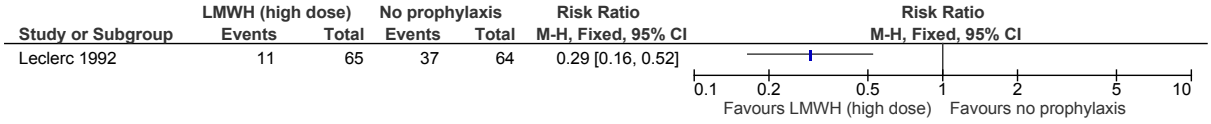
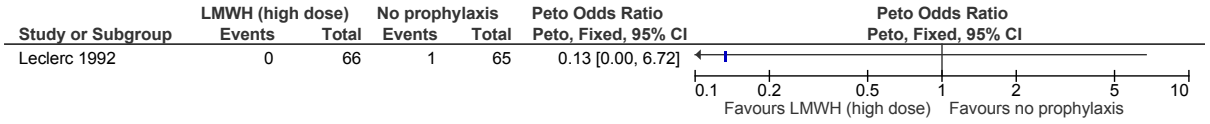


Figure 486: Major bleeding (14 days)



L.24.20 LMWH (high dose; standard duration) versus UFH

Figure 487: DVT (symptomatic and asymptomatic) (15 days)

Study or Subgroup	LMWH (high dose) Events	Total	UFH Events	Total	Risk Ratio M-H, Fixed, 95% CI
Colwell 1995D	56	145	77	143	0.72 [0.56, 0.93]

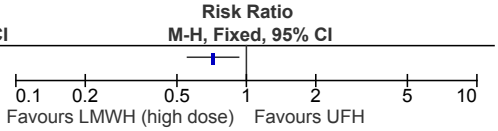


Figure 488: PE (15 days)

Study or Subgroup	LMWH (high dose) Events	Total	UFH Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Colwell 1995D	0	145	1	143	0.13 [0.00, 6.73]

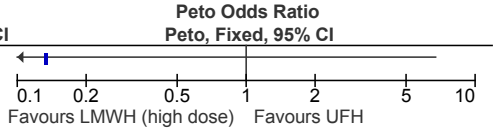
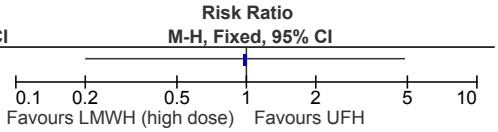


Figure 489: Major bleeding (15 days)

Study or Subgroup	LMWH (high dose) Events	Total	UFH Events	Total	Risk Ratio M-H, Fixed, 95% CI
Colwell 1995D	3	228	3	225	0.99 [0.20, 4.84]



L.24.21 LMWH (high dose; standard duration) versus VKA

Figure 490: All-cause mortality (15 days)

Study or Subgroup	LMWH (high dose) Events	Total	VKA Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fitzgerald 2001	1	173	3	176	100.0%	0.37 [0.05, 2.66]
Lassen 2007	0	109	0	109		Not estimable
Leclerc 1996	0	336	0	334		Not estimable
Total (95% CI)		**618**		**619**	**100.0%**	**0.37 [0.05, 2.66]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)

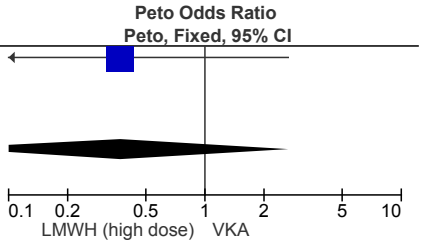


Figure 491: DVT (symptomatic and asymptomatic) (15 days)

Study or Subgroup	LMWH (high dose) Events	Total	VKA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fitzgerald 2001	44	173	79	176	36.4%	0.57 [0.42, 0.77]
Lassen 2007	15	109	29	109	13.5%	0.52 [0.29, 0.91]
Leclerc 1996	76	206	109	211	50.1%	0.71 [0.57, 0.89]
Total (95% CI)		**488**		**496**	**100.0%**	**0.63 [0.53, 0.75]**
Total events	135		217			

Heterogeneity: Chi² = 2.14, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 5.21 (P < 0.00001)

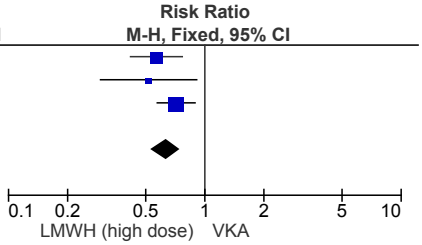


Figure 492: PE (15 days)

Study or Subgroup	LMWH (high dose) Events	Total	VKA Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fitzgerald 2001	0	173	1	176	14.4%	0.14 [0.00, 6.94]
Lassen 2007	2	109	0	109	28.6%	7.46 [0.46, 120.00]
Leclerc 1996	1	206	3	211	57.0%	0.37 [0.05, 2.68]
Total (95% CI)		**488**		**496**	**100.0%**	**0.76 [0.17, 3.37]**
Total events	3		4			

Heterogeneity: Chi² = 3.82, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 0.36 (P = 0.72)

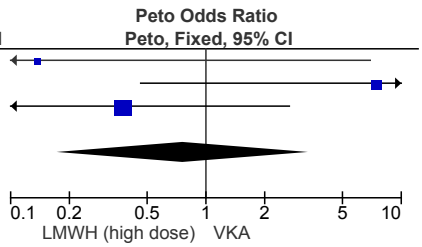


Figure 493: Major bleeding (15 days)

Study or Subgroup	LMWH (high dose) Events	Total	VKA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fitzgerald 2001	9	173	4	176	39.7%	2.29 [0.72, 7.29]
Lassen 2007	0	149	0	151		Not estimable
Leclerc 1996	7	336	6	334	60.3%	1.16 [0.39, 3.41]
Total (95% CI)		**658**		**661**	**100.0%**	**1.61 [0.74, 3.51]**
Total events	16		10			

Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)

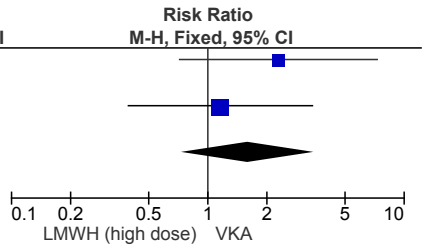


Figure 494: Fatal PE (12±2 days)

Study or Subgroup	LMWH (high dose) Events	Total	VKA Events	Total	Risk Difference M-H, Fixed, 95% CI
Lassen 2007	0	109	0	109	0.00 [-0.02, 0.02]

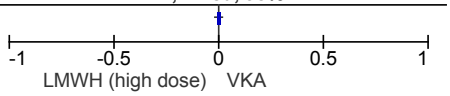


Figure 495: Wound haematoma (14 days)

Study or Subgroup	LMWH (high dose) Events	Total	VKA Events	Total	Risk Ratio M-H, Fixed, 95% CI
Leclerc 1996	1	336	1	334	0.99 [0.06, 15.83]

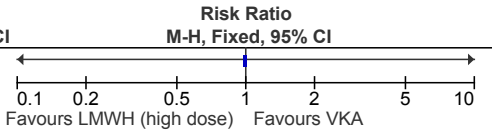
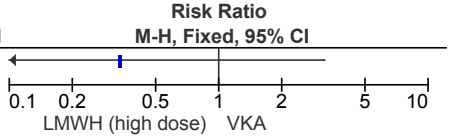


Figure 496: Wound infection (12±2 days)

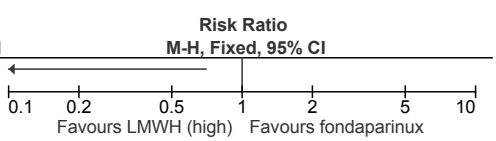
Study or Subgroup	LMWH (high dose) Events	Total	VKA Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lassen 2007	1	149	3	151	0.34 [0.04, 3.21]



L.24.22 LMWH (high dose; standard duration) versus fondaparinux

Figure 497: Major bleeding (49 days)

Study or Subgroup	LMWH (high dose) Events	Total	Fondaparinux Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bauer 2001	1	517	11	517	0.09 [0.01, 0.70]



L.24.23 LMWH (high dose; standard duration)+ AES versus fondaparinux + AES

Figure 498: All-cause mortality (49 days)

Study or Subgroup	LMWH (high dose) + AES Events	Total	Fondaparinux + AES Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bauer 2001	3	517	2	517	1.50 [0.25, 8.94]

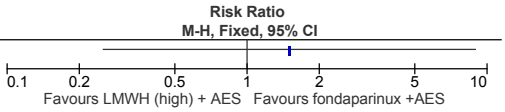


Figure 499: DVT (symptomatic and asymptomatic) (49 days)

Study or Subgroup	LMWH (high dose) + AES Events	Total	Fondaparinux + AES Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bauer 2001	98	361	45	361	2.18 [1.58, 3.00]

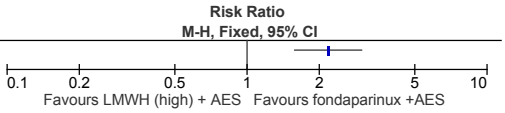


Figure 500: PE (49 days)

Study or Subgroup	LMWH (high dose) + AES Events	Total	Fondaparinux + AES Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bauer 2001	4	517	1	517	4.00 [0.45, 35.67]

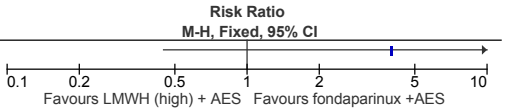
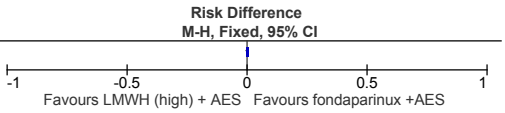


Figure 501: Fatal PE (49 days)

Study or Subgroup	LMWH (high dose) + AES Events	Total	Fondaparinux + AES Events	Total	Risk Difference M-H, Fixed, 95% CI
Bauer 2001	0	517	0	517	0.00 [-0.00, 0.00]



L.24.24 LMWH (high dose; standard duration) versus apixaban

Figure 502: All-cause mortality (60 days)

Study or Subgroup	LMWH (high) Events	Total	Apixaban Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lassen 2007	0	109	1	208	25.8%	0.63 [0.03, 15.42]
Lassen 2009	6	1569	3	1599	74.2%	2.04 [0.51, 8.14]
Total (95% CI)		**1678**		**1807**	**100.0%**	**1.68 [0.48, 5.79]**
Total events	6		4			

Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)

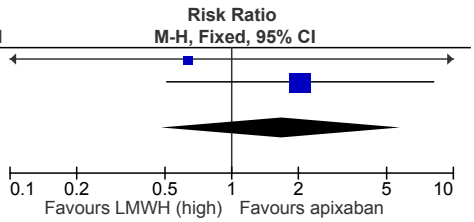


Figure 503: DVT (symptomatic and asymptomatic) (14 days)

Study or Subgroup	LMWH (high) Events	Total	Apixaban Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lassen 2007	15	109	21	208	14.1%	1.36 [0.73, 2.54]
Lassen 2009	92	1122	89	1142	85.9%	1.05 [0.80, 1.39]
Total (95% CI)		**1231**		**1350**	**100.0%**	**1.10 [0.85, 1.41]**
Total events	107		110			

Heterogeneity: Chi² = 0.56, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)

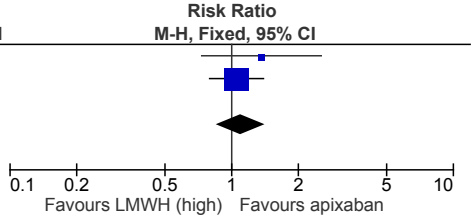


Figure 504: PE (14 days)

Study or Subgroup	LMWH (high) Events	Total	Apixaban Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lassen 2007	2	109	0	208	34.5%	9.50 [0.46, 196.15]
Lassen 2009	10	1596	15	1599	65.5%	0.67 [0.30, 1.48]
Total (95% CI)		**1705**		**1807**	**100.0%**	**1.67 [0.14, 20.28]**
Total events	12		15			

Heterogeneity: Tau² = 2.31; Chi² = 2.81, df = 1 (P = 0.09); I² = 64%
Test for overall effect: Z = 0.40 (P = 0.69)

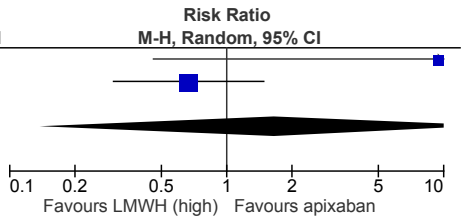


Figure 505: Major bleeding (14 days)

Study or Subgroup	LMWH (high) Events	Total	Apixaban Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lassen 2007	0	149	4	305	28.8%	0.23 [0.01, 4.18]
Lassen 2009	22	1588	11	1596	71.2%	2.01 [0.98, 4.13]
Total (95% CI)		**1737**		**1901**	**100.0%**	**1.07 [0.15, 7.63]**
Total events	22		15			

Heterogeneity: Tau² = 1.27; Chi² = 2.08, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 0.07 (P = 0.94)

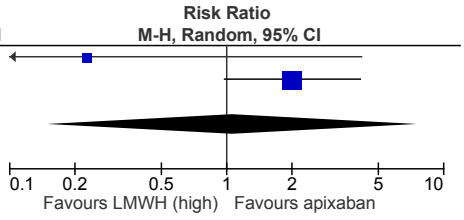


Figure 506: Fatal PE (14 days)

Study or Subgroup	LMWH (high) Events	Total	Apixaban Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lassen 2007	0	109	1	208	34.1%	0.63 [0.03, 15.42]
Lassen 2009	2	1596	2	1599	65.9%	1.00 [0.14, 7.10]
Total (95% CI)		**1705**		**1807**	**100.0%**	**0.88 [0.17, 4.62]**
Total events	2		3			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.88)

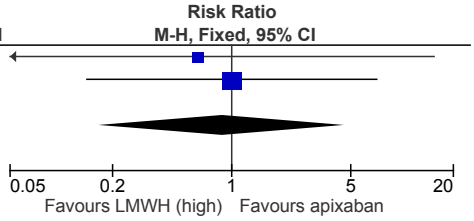


Figure 507: Clinically relevant non-major bleeding (14 days)

Study or Subgroup	LMWH (high) Events	Total	Apixaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lassen 2009	47	1588	35	1596	1.35 [0.88, 2.08]

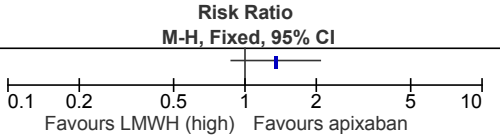
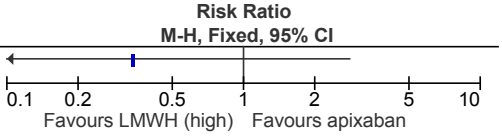


Figure 508: Wound infection (14 days)

Study or Subgroup	LMWH (high) Events	Total	Apixaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lassen 2007	1	149	6	305	0.34 [0.04, 2.81]



L.24.25 LMWH (high dose; standard duration) versus dabigatran

Figure 509: All-cause mortality (18 days)

Study or Subgroup	LMWH (high dose) Events	Total	Dabigatran Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Ginsberg 2009	0	868	1	857	0.13 [0.00, 6.73]

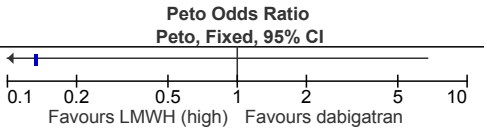


Figure 510: DVT (symptomatic and asymptomatic) (18 days)

Study or Subgroup	LMWH (high dose) Events	Total	Dabigatran Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ginsberg 2009	158	643	181	604	0.82 [0.68, 0.98]

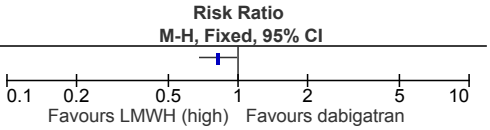


Figure 511: PE (18 days)

Study or Subgroup	LMWH (high dose) Events	Total	Dabigatran Events	Total	Risk Ratio IV, Fixed, 95% CI
Ginsberg 2009	5	643	6	604	0.78 [0.24, 2.55]

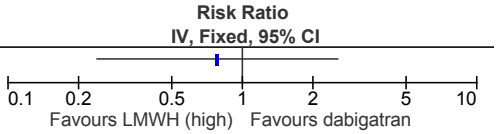


Figure 512: Major bleeding (18 days)

Study or Subgroup	LMWH (high dose) Events	Total	Dabigatran Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ginsberg 2009	12	868	5	857	2.37 [0.84, 6.70]

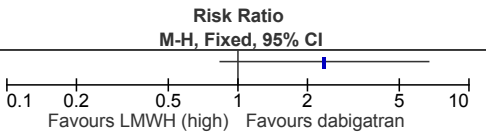
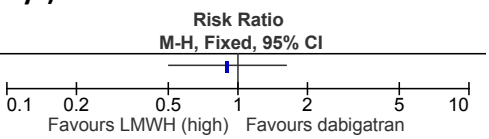


Figure 513: Clinically relevant non-major bleeding (18 days)

Study or Subgroup	LMWH (high dose) Events	Total	Dabigatran Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ginsberg 2009	21	868	23	857	0.90 [0.50, 1.62]



L.24.26 LMWH (high dose; standard duration) versus rivaroxaban

Figure 514: All-cause mortality (35 days)

Study or Subgroup	LMWH (high dose) Events	Total	Rivaroxaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Turpie 2009	3	1508	4	1526	0.76 [0.17, 3.39]

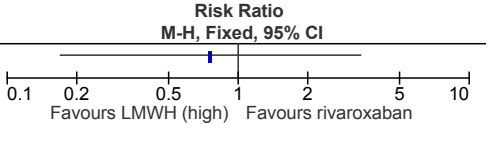


Figure 515: DVT (symptomatic and asymptomatic) (17 days)

Study or Subgroup	LMWH (high dose) Events	Total	Rivaroxaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Turpie 2009	86	959	61	965	1.42 [1.03, 1.95]

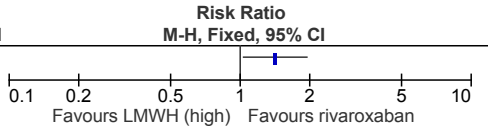


Figure 516: PE (17 days)

Study or Subgroup	LMWH (high dose) Events	Total	Rivaroxaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Turpie 2009	8	1508	4	1526	2.02 [0.61, 6.71]

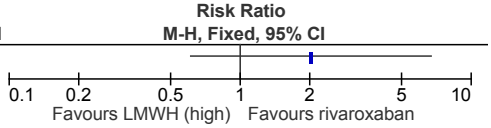


Figure 517: Major bleeding (17 days)

Study or Subgroup	LMWH (high dose) Events	Total	Rivaroxaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Turpie 2009	16	1564	27	1584	0.60 [0.32, 1.11]

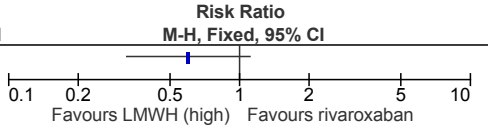


Figure 518: Fatal PE (17 days)

Study or Subgroup	LMWH (high dose) Events	Total	Rivaroxaban Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Turpie 2009	0	1508	1	1526	0.14 [0.00, 6.90]

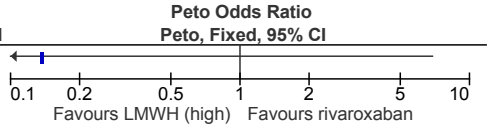


Figure 519: Clinically relevant non-major bleeding (17 days)

Study or Subgroup	LMWH (high dose) Events	Total	Rivaroxaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Turpie 2009	30	1508	39	1526	0.78 [0.49, 1.25]

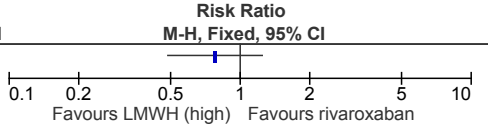
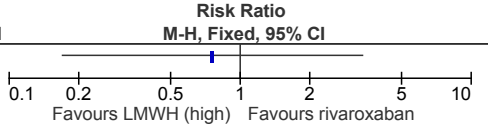


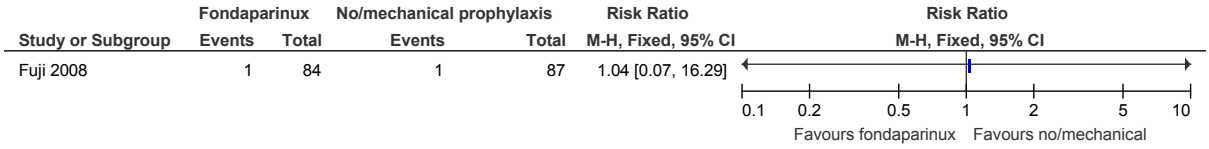
Figure 520: Wound infection (17 days)

Study or Subgroup	LMWH (high dose) Events	Total	Rivaroxaban Events	Total	Risk Ratio M-H, Fixed, 95% CI
Turpie 2009	3	1508	4	1526	0.76 [0.17, 3.39]



L.24.27 Fondaparinux versus no pharmacological prophylaxis

Figure 521: **Major bleeding (11-17 days)**



No prophylaxis and mechanical prophylaxis lumped together for bleeding outcomes

L.24.28 Fondaparinux + AES versus AES

Figure 522: All-cause mortality (11-17 days)

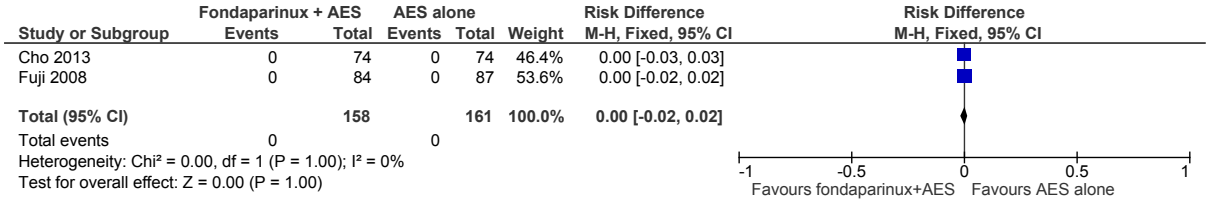


Figure 523: DVT (symptomatic and asymptomatic) (7 days)

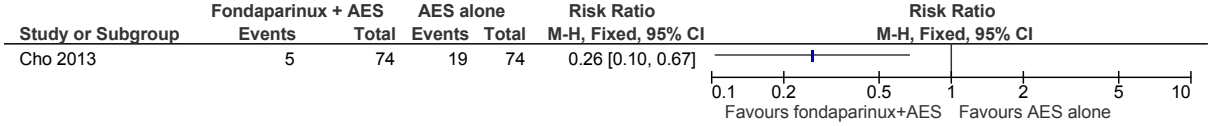
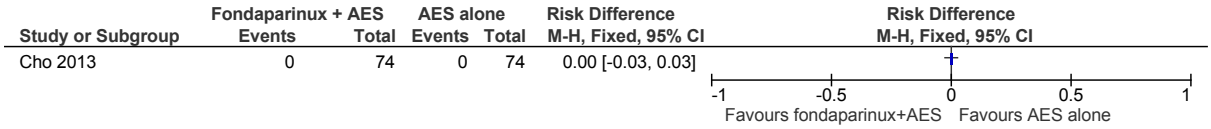


Figure 524: PE (7 days)



L.24.29 Fondaparinux + IPCD + AES versus VKA + IPCD + AES

Figure 525: All-cause mortality (30 days)

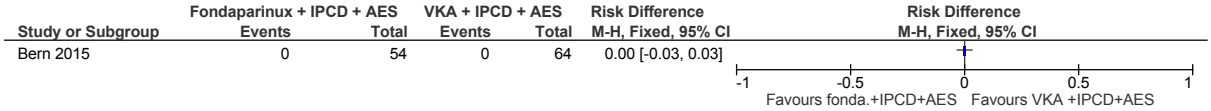


Figure 526: DVT (symptomatic and asymptomatic) (30 days)

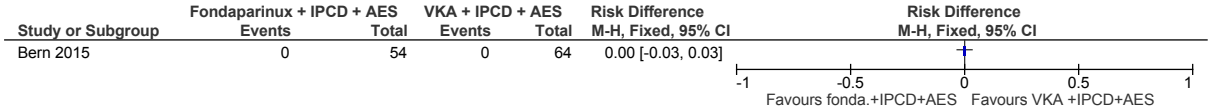
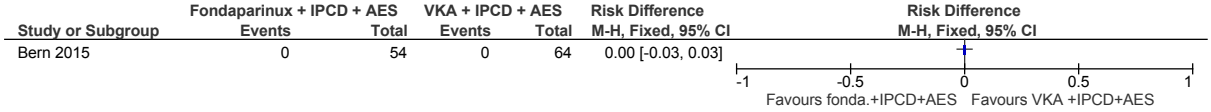


Figure 527: PE (30 days)



L.24.30 Apixaban versus VKA

Figure 528: All-cause mortality (12±2 days)

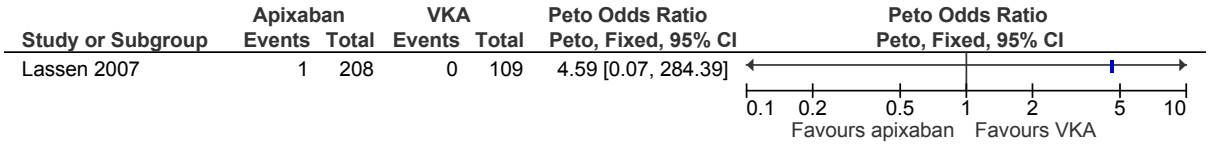


Figure 529: DVT (symptomatic and asymptomatic) (12±2 days)

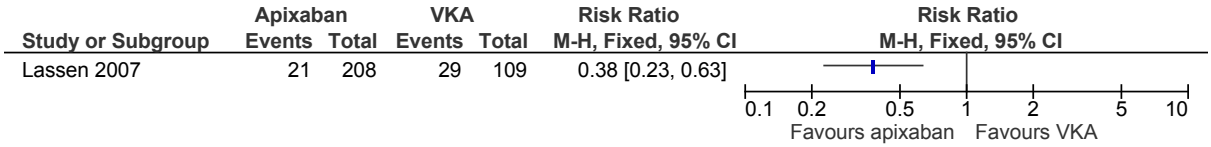


Figure 530: PE (12±2 days)

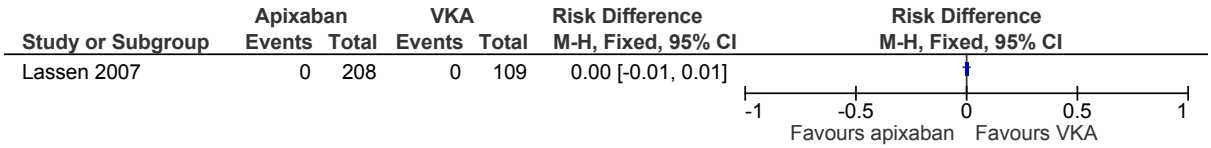


Figure 531: Major bleeding (12±2 days)

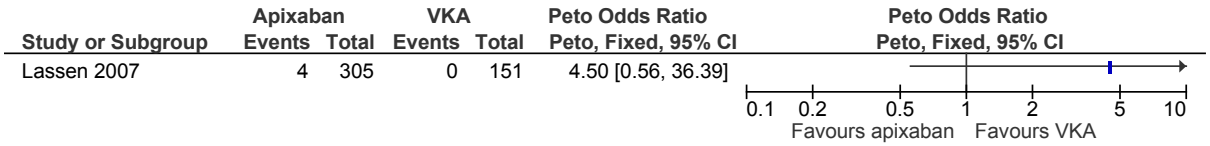


Figure 532: Fatal PE (12±2 days)

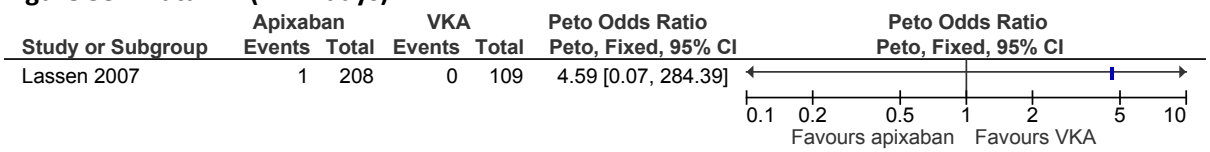
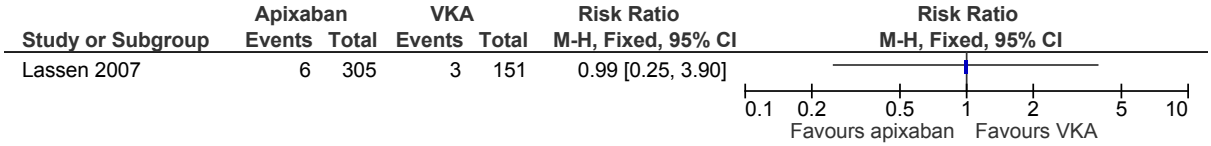


Figure 533: Wound infection



L.24.31 Dabigatran versus no prophylaxis

Figure 534: All-cause mortality (14 days)

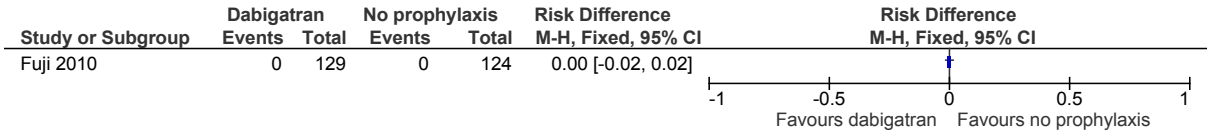


Figure 535: DVT (symptomatic and asymptomatic) (14 days)

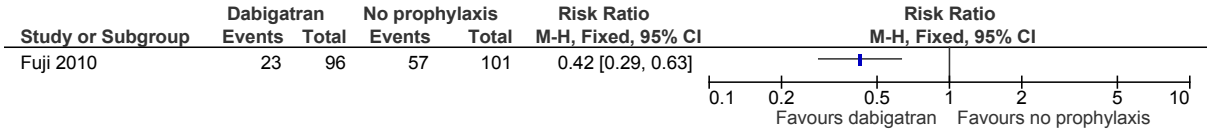


Figure 536: PE (14 days)

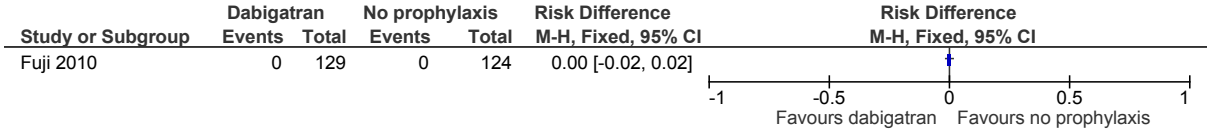


Figure 537: Major bleeding (14 days)

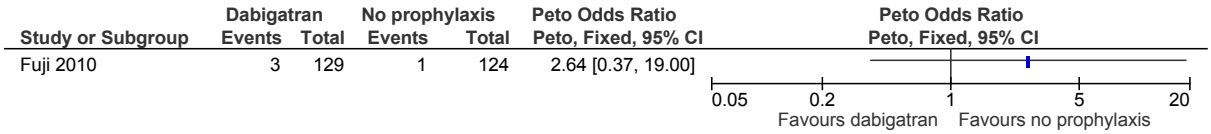
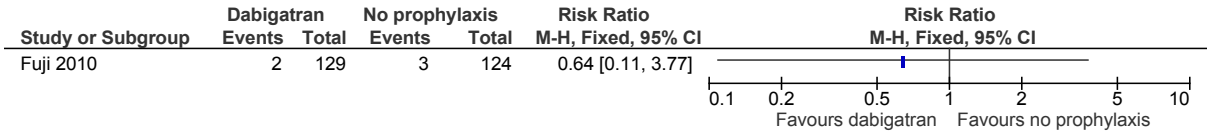


Figure 538: Clinically relevant non-major bleeding (14 days)



L.24.32 Rivaroxaban versus aspirin

Figure 539: DVT (symptomatic and asymptomatic) (28 days)

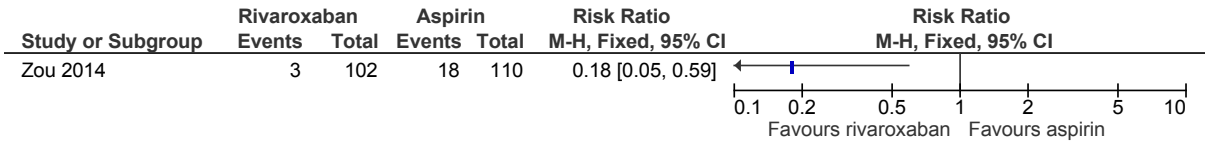
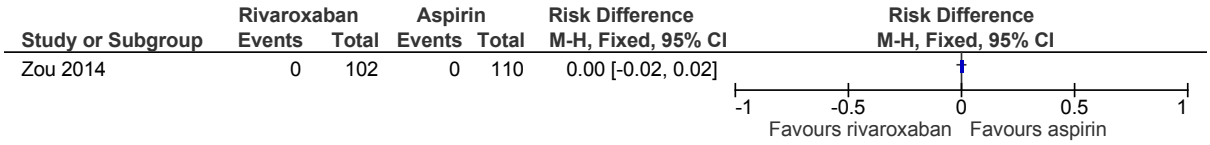


Figure 540: PE (28 days)



L.24.33 Foot pump versus no prophylaxis

Figure 541: DVT (symptomatic and asymptomatic) (10 days)

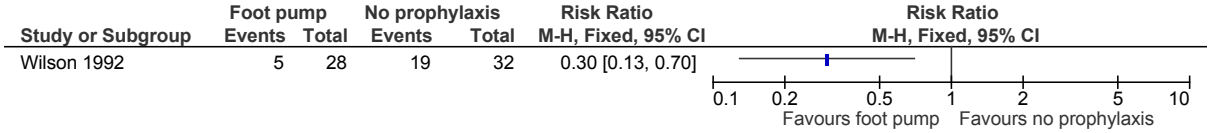
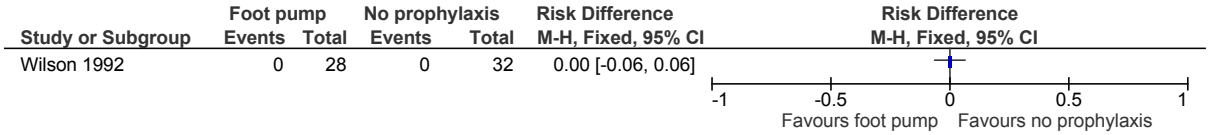


Figure 542: PE (time-point not reported)



L.24.34 AES versus no prophylaxis

Figure 543: DVT (symptomatic and asymptomatic) (30 days)

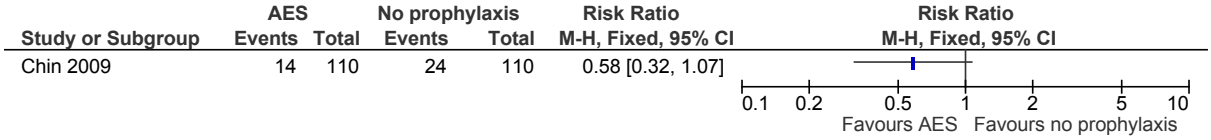


Figure 544: PE (30 days)

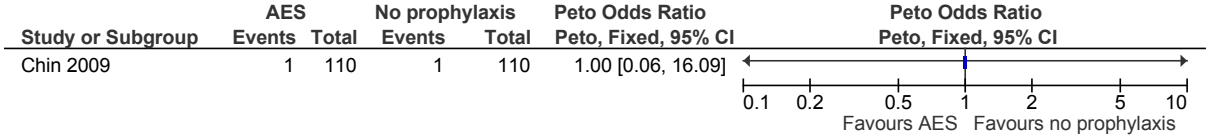


Figure 545: Major bleeding (time-point not reported)

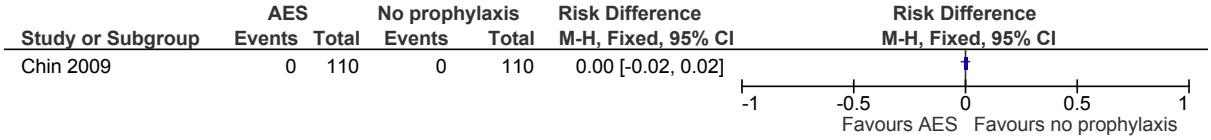


Figure 546: Technical complications of mechanical interventions (time-point not reported)

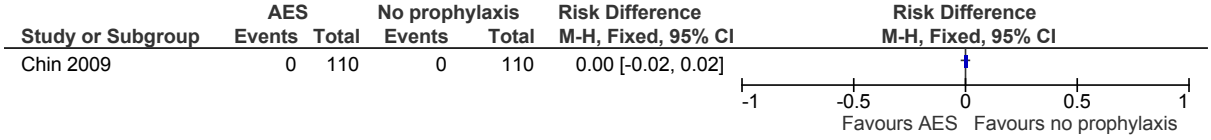
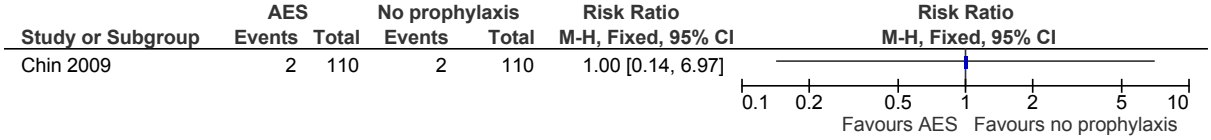


Figure 547: Wound infection (30 days)



L.24.35 IPCD versus no prophylaxis

Figure 548: DVT (symptomatic and asymptomatic) (30 days)

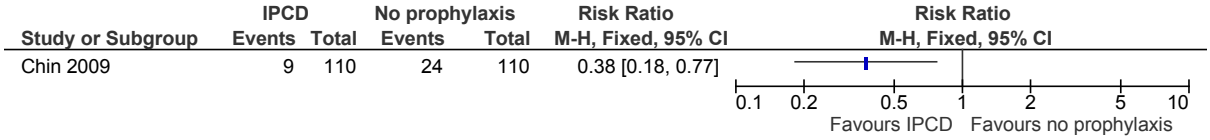


Figure 549: PE (30 days)

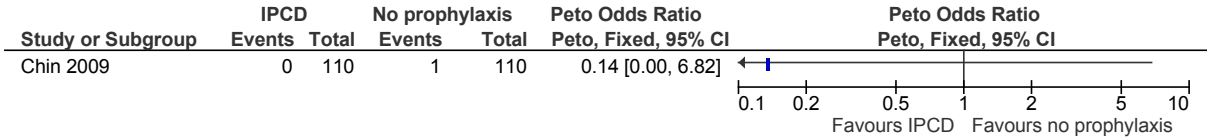


Figure 550: Major bleeding (time-point not reported)

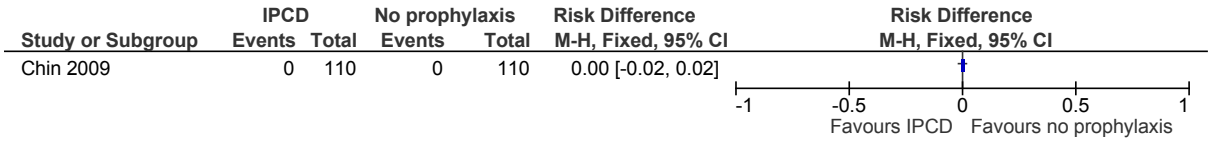


Figure 551: Technical complications of mechanical interventions (time-point not reported)

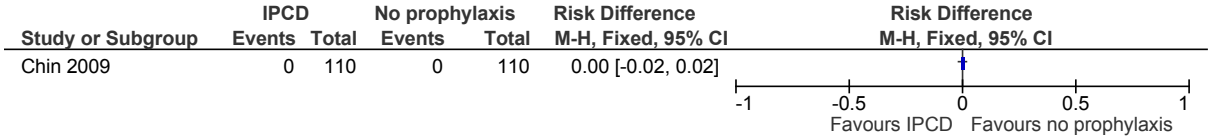
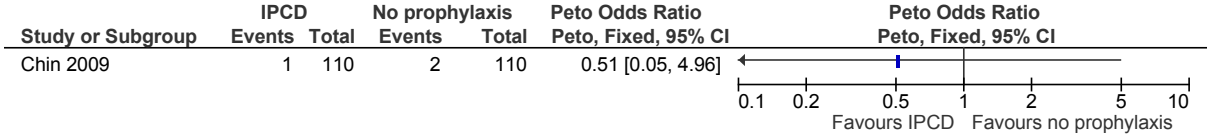


Figure 552: Wound infection (30 days)



L.24.36 IPCD versus AES

Figure 553: DVT (symptomatic and asymptomatic) (30 days)

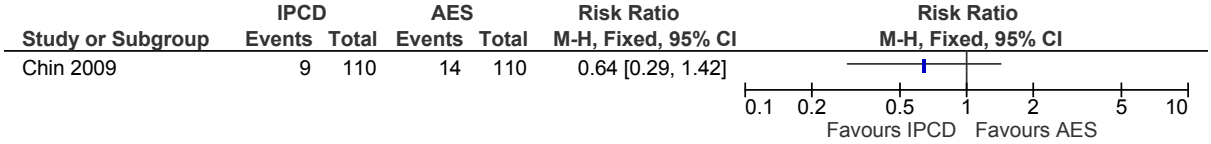


Figure 554: PE (30 days)

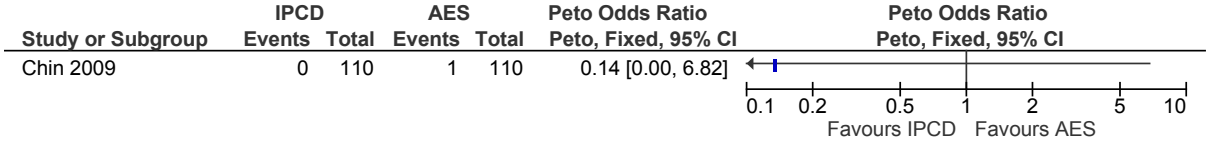


Figure 555: Major bleeding (time-point not reported)

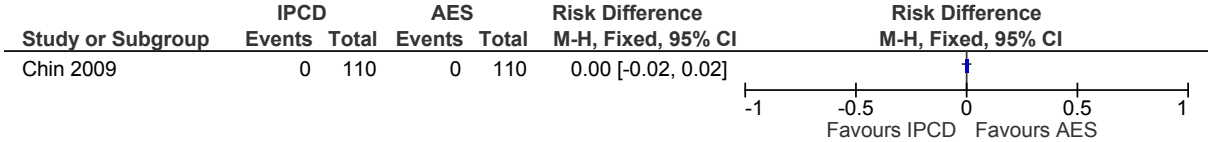


Figure 556: Technical complications of mechanical interventions (time-point not reported)

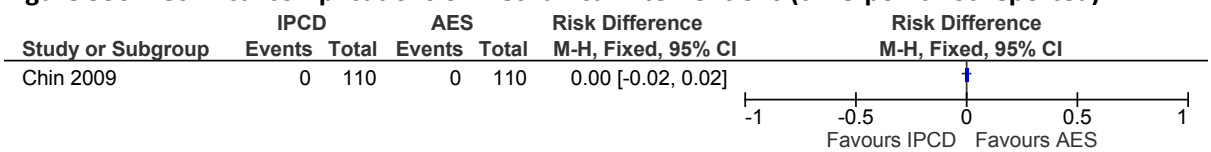
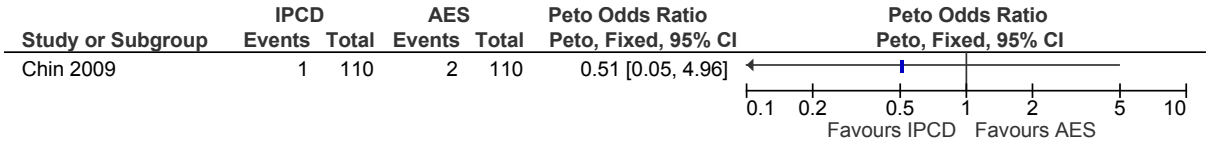
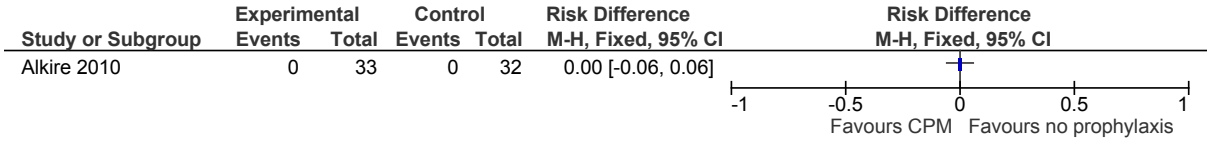


Figure 557: Wound infection (30 days)



L.24.37 CPM versus no prophylaxis

Figure 558: DVT (symptomatic and asymptomatic) (90 days)



L.25 Non-arthroplasty orthopaedic knee surgery

L.25.1 Overall population stratum

L.25.1.1 LMWH (standard dose, extended duration) versus LMWH (standard dose, standard duration)

Figure 559: DVT (23-28 days)

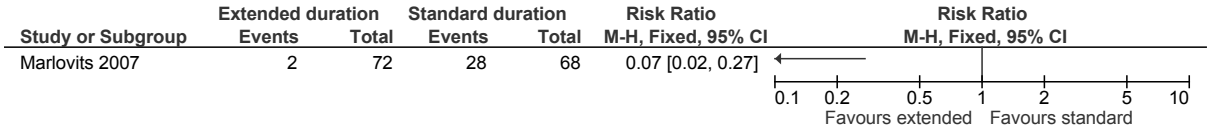


Figure 560: PE (23-28 days)

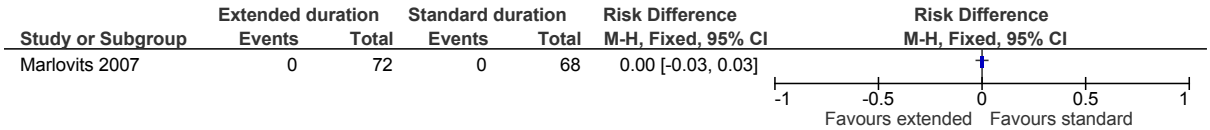
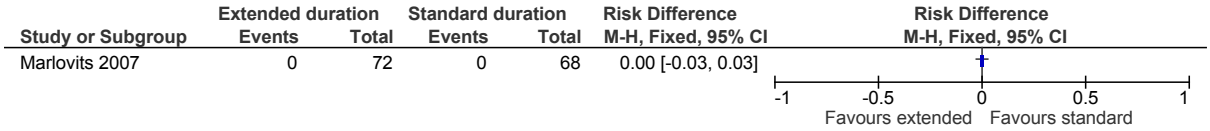


Figure 561: Major bleeding (23-28 days)



L.25.1.2 LMWH (high dose, standard duration) versus AES (full length)

Figure 562: All-cause mortality (8 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Risk Difference M-H, Fixed, 95% CI
Camporese 2008	0	657	0	660	0.00 [-0.00, 0.00]

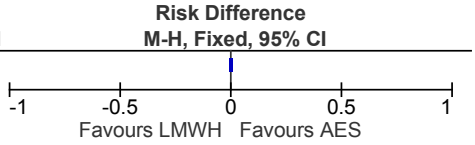


Figure 563: DVT (8 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Risk Ratio M-H, Fixed, 95% CI
Camporese 2008	10	657	29	660	0.35 [0.17, 0.70]

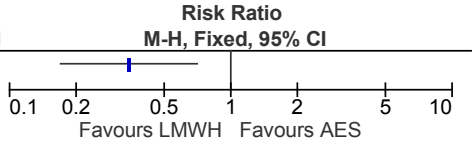


Figure 564: PE (8 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Peto Odds Ratio Peto, Fixed, 95% CI
Camporese 2008	2	657	2	660	1.00 [0.14, 7.15]

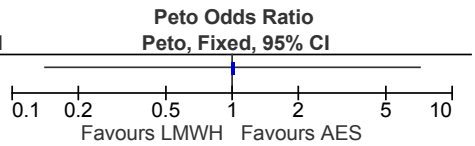
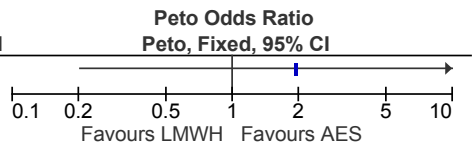


Figure 565: Major bleeding (8 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Peto Odds Ratio Peto, Fixed, 95% CI
Camporese 2008	2	657	1	660	1.96 [0.20, 18.86]



L.25.1.3 LMWH (high dose, extended duration) versus AES (full length)

Figure 566: All-cause mortality (8 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Risk Difference M-H, Fixed, 95% CI
Camporese 2008	0	444	0	660	0.00 [-0.00, 0.00]

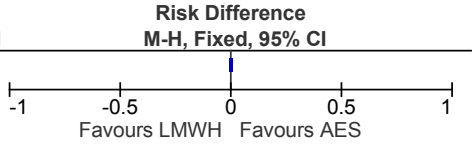


Figure 567: DVT (8 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Risk Ratio M-H, Fixed, 95% CI
Camporese 2008	9	444	29	660	0.46 [0.22, 0.97]

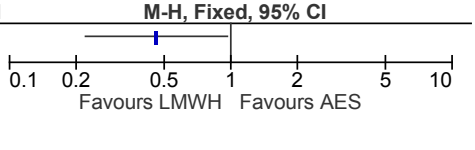


Figure 568: PE

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Peto Odds Ratio Peto, Fixed, 95% CI
Camporese 2008	2	444	2	660	1.50 [0.20, 11.13]

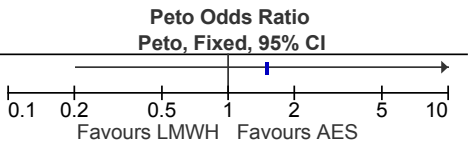
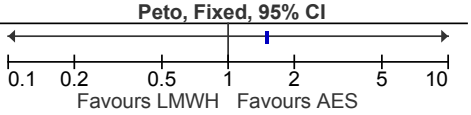


Figure 569: Major bleeding (8 days)

Study or Subgroup	LMWH Events	LMWH Total	AES Events	AES Total	Peto Odds Ratio Peto, Fixed, 95% CI
Camporese 2008	1	444	1	660	1.50 [0.09, 25.41]



L.25.1.4 LMWH (high dose, extended duration) versus LMWH (high dose, standard duration)

Figure 570: All-cause mortality (8 days)

Study or Subgroup	Extended duration Events	Extended duration Total	Standard duration Events	Standard duration Total	Risk Difference M-H, Fixed, 95% CI
Camporese 2008	0	444	0	657	0.00 [-0.00, 0.00]

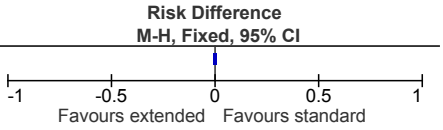


Figure 571: DVT (8 days)

Study or Subgroup	Extended duration Events	Extended duration Total	Standard duration Events	Standard duration Total	Risk Ratio M-H, Fixed, 95% CI
Camporese 2008	9	444	10	657	1.33 [0.55, 3.25]

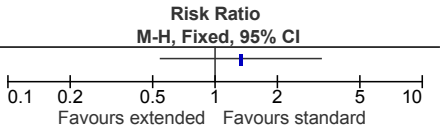


Figure 572: PE (8 days)

Study or Subgroup	Extended duration Events	Extended duration Total	Standard duration Events	Standard duration Total	Peto Odds Ratio Peto, Fixed, 95% CI
Camporese 2008	2	444	2	657	1.50 [0.20, 11.06]

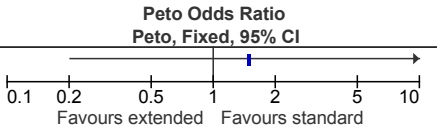
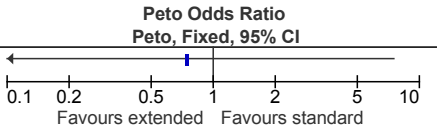


Figure 573: Major bleeding (8 days)

Study or Subgroup	Extended duration Events	Extended duration Total	Standard duration Events	Standard duration Total	Peto Odds Ratio Peto, Fixed, 95% CI
Camporese 2008	1	444	2	657	0.75 [0.07, 7.52]



L.25.1.5 Rivaroxaban versus no prophylaxis

Figure 574: All-cause mortality (90 days)

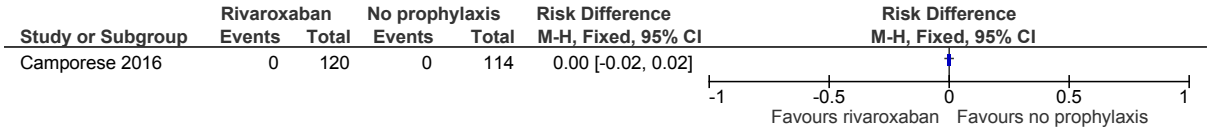


Figure 575: DVT (90 days)

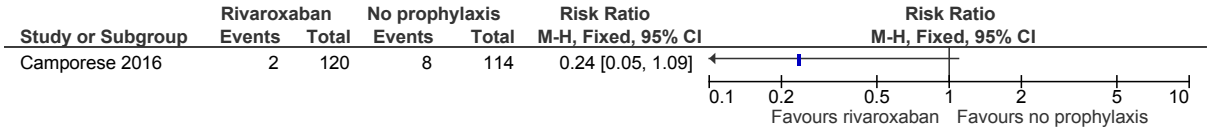


Figure 576: PE (90 days)

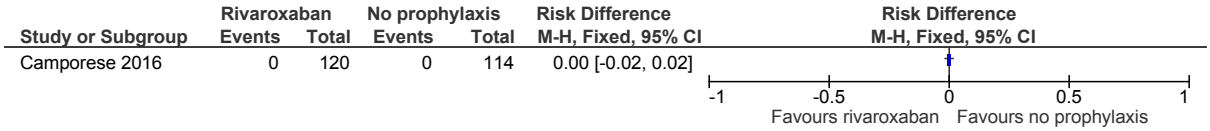
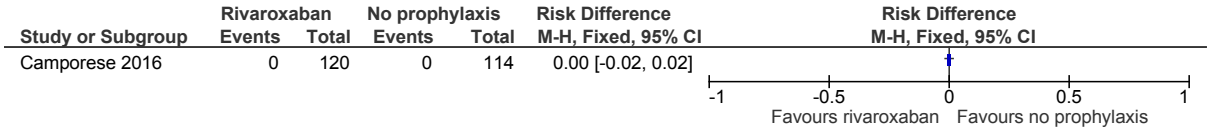


Figure 577: Fatal PE (90 days)



L.25.2 Major arthroscopic surgery stratum

L.25.2.1 LMWH (low dose; standard duration) versus no prophylaxis

Figure 578: DVT (10 days)

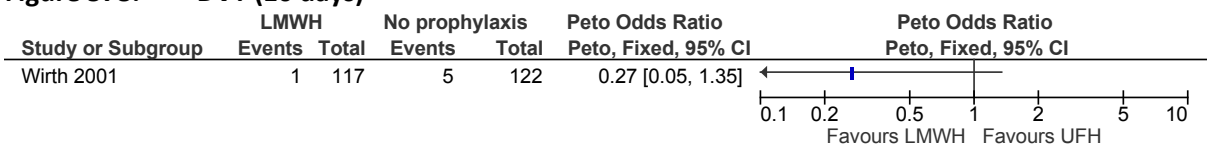


Figure 579: PE (10 days)

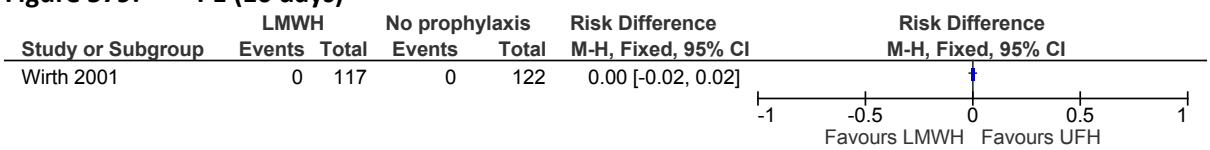


Figure 580: Major bleeding (10 days)

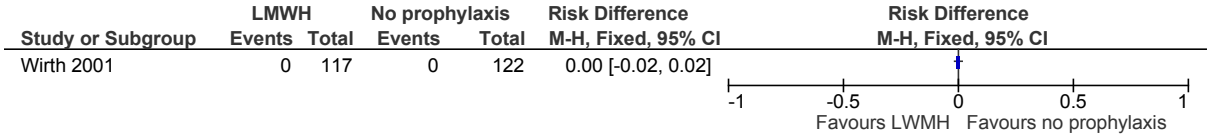
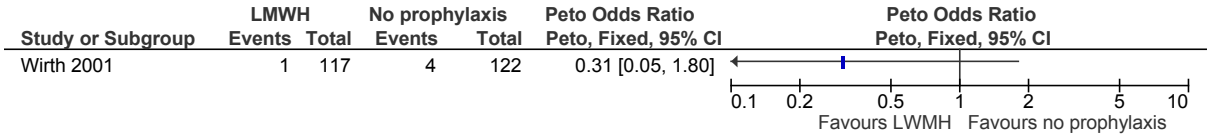


Figure 581: Clinically relevant non-major bleeding (10 days)



L.25.3 Minor arthroscopic surgery stratum

L.25.3.1 LMWH (low dose; standard duration) versus no prophylaxis

Figure 582: All-cause mortality (90 days)

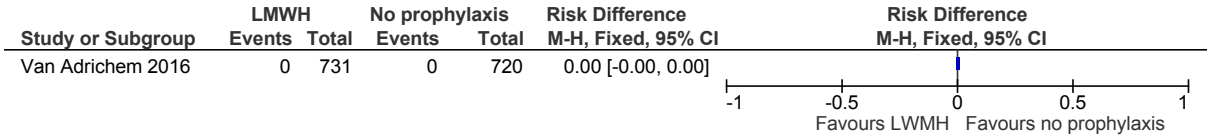
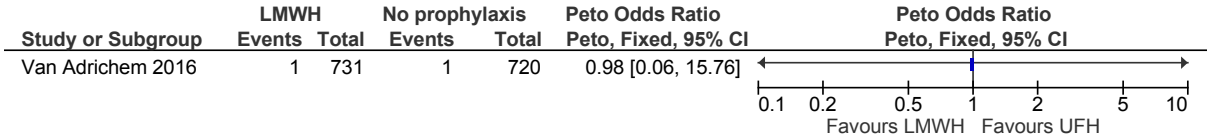


Figure 583: PE (90 days)



L.26 Foot and ankle orthopaedic surgery

No relevant clinical studies were identified.

L.27 Upper limb orthopaedic surgery

No relevant clinical studies were identified.

L.28 Spinal surgery

L.28.1 LMWH (standard dose; standard duration) versus rivaroxaban

Figure 584: All-cause mortality (14 days)

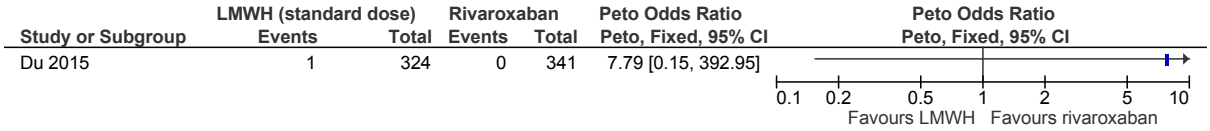


Figure 585: DVT (symptomatic and asymptomatic) (14 days)

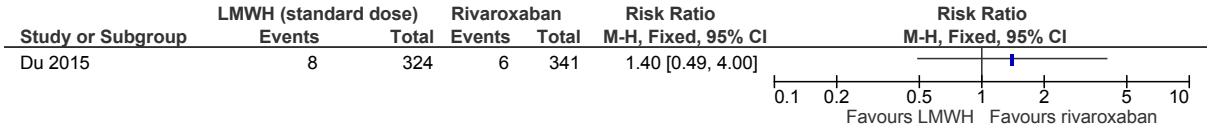


Figure 586: PE (14 days)

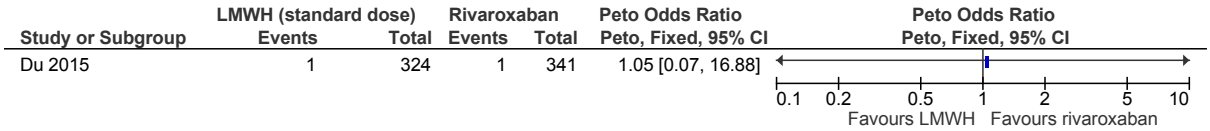


Figure 587: Major bleeding (14 days)

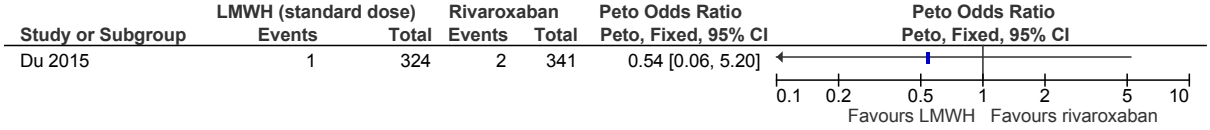
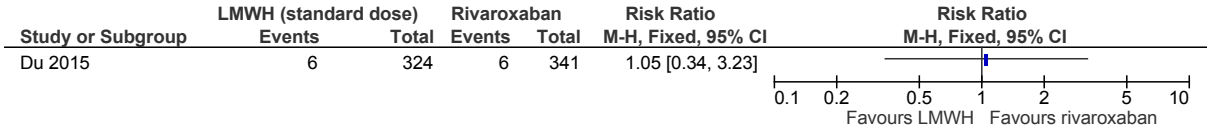


Figure 588: Clinically relevant non-major bleeding (14 days)



L.28.2 Foot pump + AES (above-knee) versus IPCD (thigh-length) + AES (above-knee)

Figure 589: DVT (symptomatic and asymptomatic) (5-7 days)

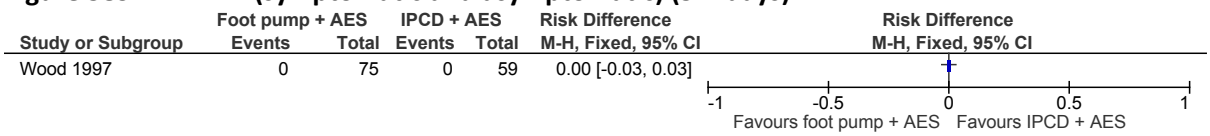


Figure 590: PE (5-7 days)

Study or Subgroup	Foot pump + AES Events	Total	IPCD + AES Events	Total	Risk Difference M-H, Fixed, 95% CI
Wood 1997	0	75	0	59	0.00 [-0.03, 0.03]

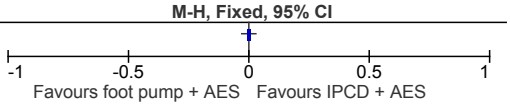
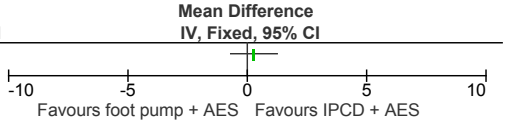


Figure 591: Visual analogue comfort scale (hospital discharge; time-point not reported)

Study or Subgroup	Foot pump + AES Mean	SD	Total	IPCD + AES Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Wood 1997	5.84	2.8	75	5.56	2.9	59	0.28 [-0.69, 1.25]



L.29 Cranial surgery

L.29.1 Strata: People undergoing intracranial surgery (non-tumour specific)

L.29.1.1 LMWH (low dose; standard duration) versus UFH

Figure 592: All-cause mortality (30 days)

Study or Subgroup	LMWH (low dose) Events	Total	UFH Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Macdonald 2003	0	51	1	49	0.13 [0.00, 6.55]

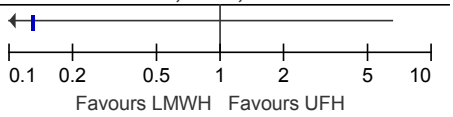


Figure 593: DVT (7 days)

Study or Subgroup	LMWH (low dose) Events	Total	UFH Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Macdonald 2003	2	51	0	49	7.25 [0.45, 117.60]

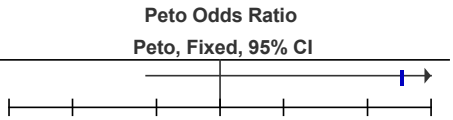


Figure 594: PE (30 days)

Study or Subgroup	LMWH (low dose) Events	Total	UFH Events	Total	Risk Difference M-H, Fixed, 95% CI
Macdonald 2003	0	51	0	49	0.00 [-0.04, 0.04]

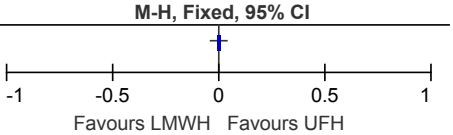


Figure 595: Fatal PE (30 days)

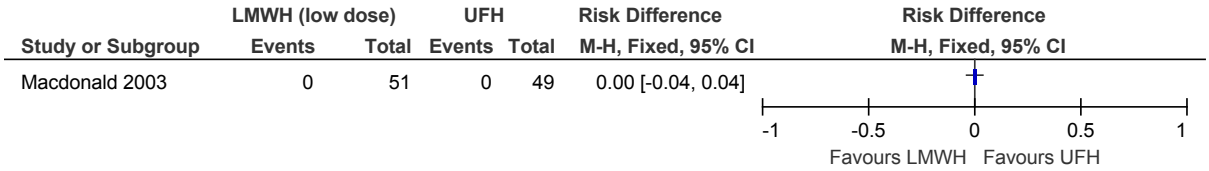


Figure 596: Major bleeding (30 days)

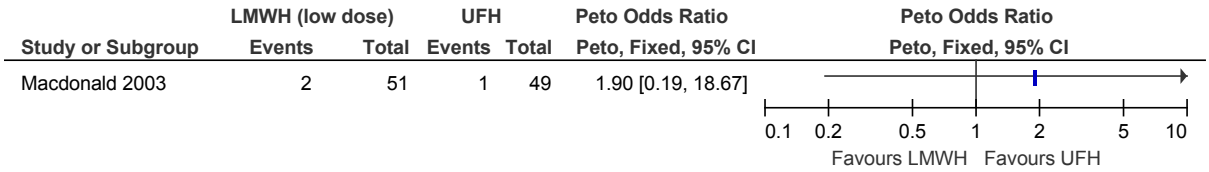
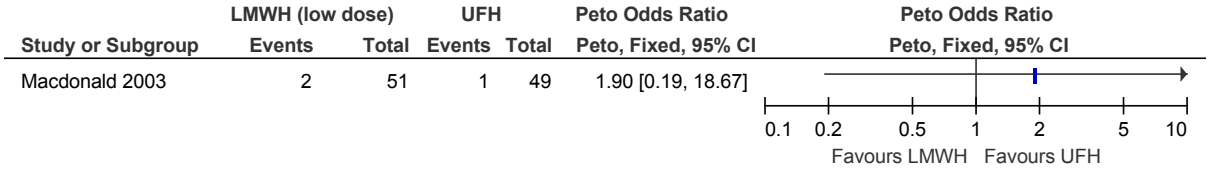


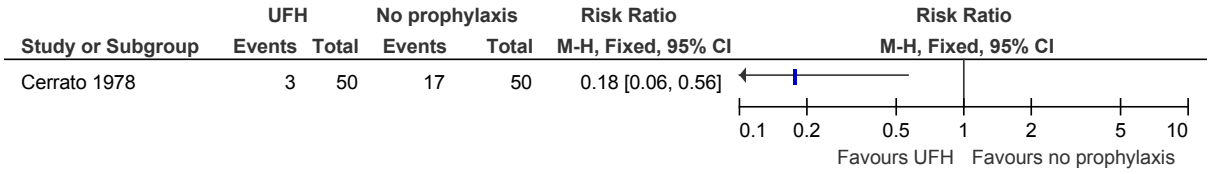
Figure 597: Thrombocytopenia (30 days)



L.29.2 Strata: People with intracranial tumour having neurosurgery

L.29.2.1 UFH versus no VTE prophylaxis

Figure 598: DVT (8 days)



L.29.2.2 LMWH (high dose; standard duration)+IPCD versus IPCD

Figure 599: All-cause mortality (30 days)

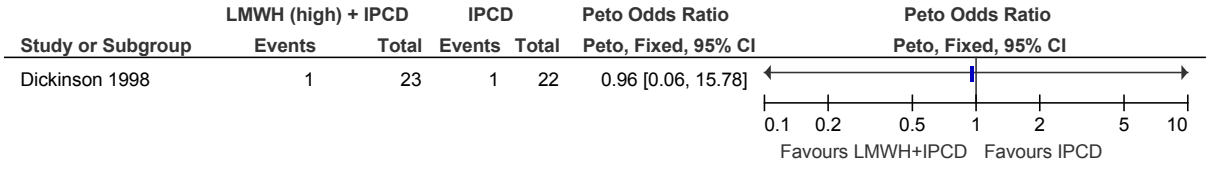


Figure 600: DVT (30 days)

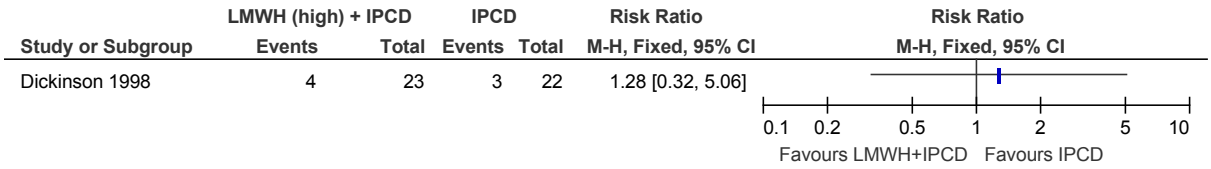


Figure 601: PE (30 days)

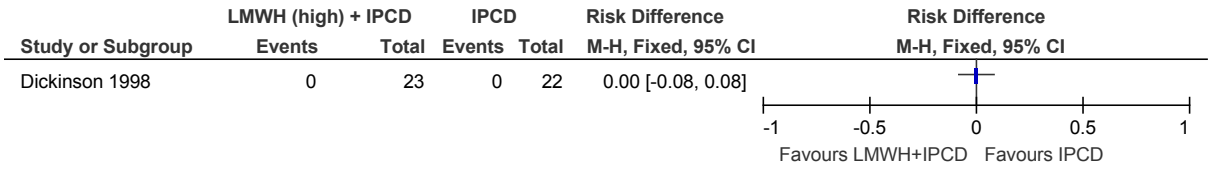


Figure 602: Fatal PE (30 days)

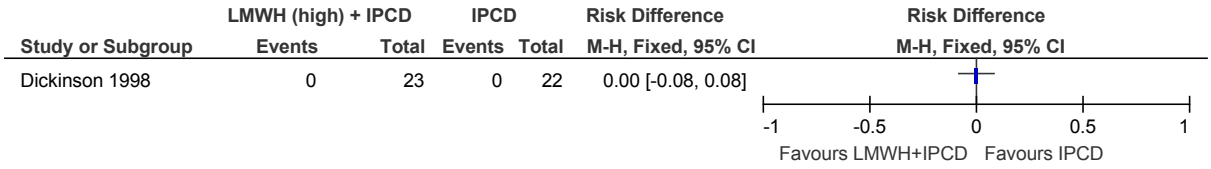
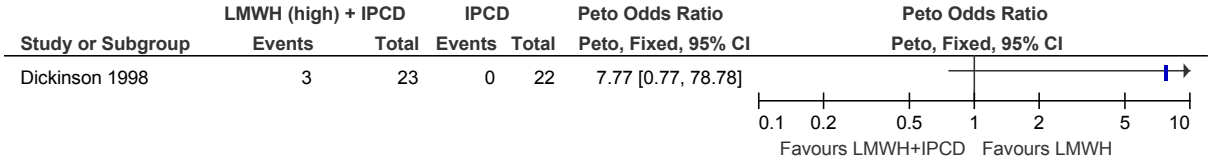


Figure 603: Major bleeding (30 days)



L.29.2.3 LMWH (standard dose; standard duration) + IPCD versus UFH + IPCD

Figure 604: All-cause mortality (30 days)

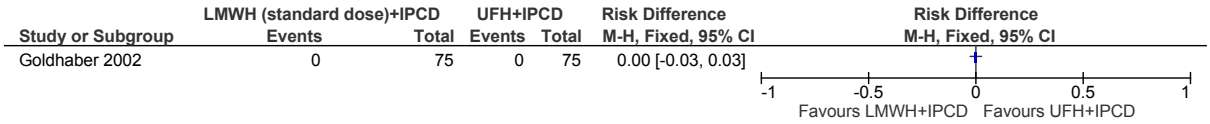


Figure 605: DVT (30 days)

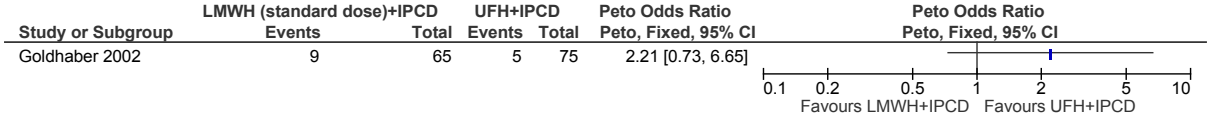
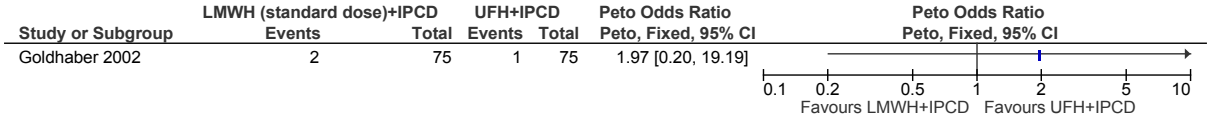


Figure 606: Major bleeding (30 days)



L.29.2.4 LMWH (high dose; standard duration) versus IPCD

Figure 607: All-cause mortality (30 days)

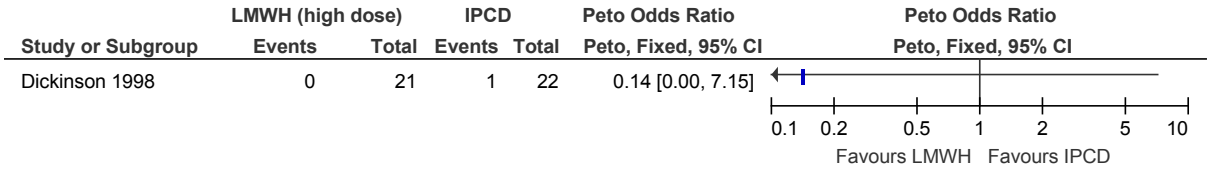


Figure 608: DVT (30 days)

Figure 609: PE (30 days)

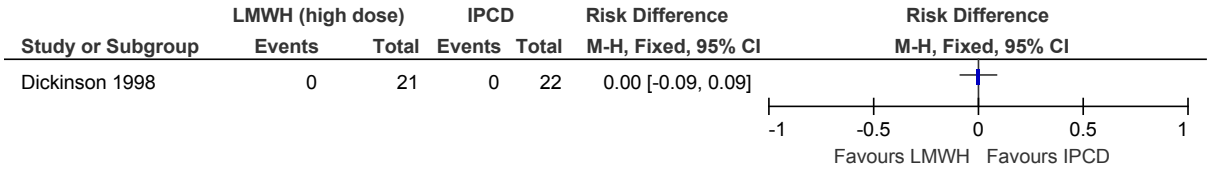


Figure 610: Fatal PE (30 days)

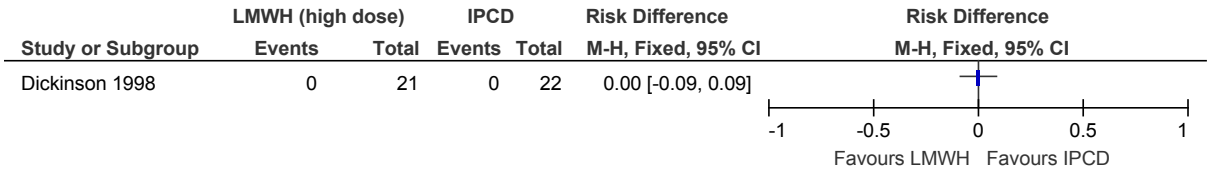
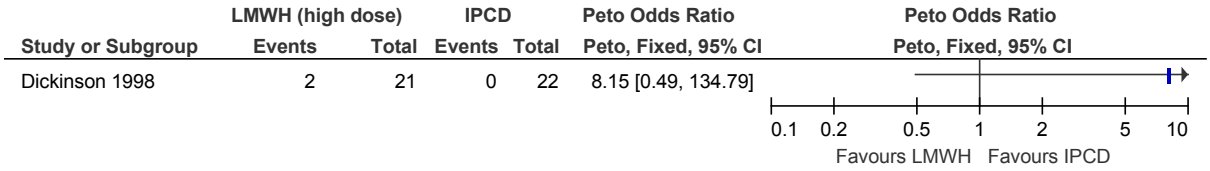


Figure 611: Major bleeding (30 days)



L.29.2.5 IPCD + AES versus AES alone

Figure 612: DVT (symptomatic and asymptomatic) (8-10 days)

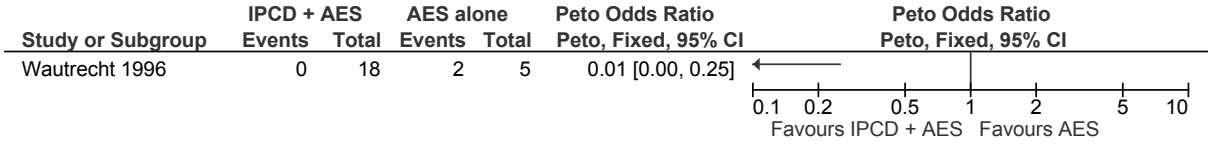


Figure 613: PE (8-10 days)

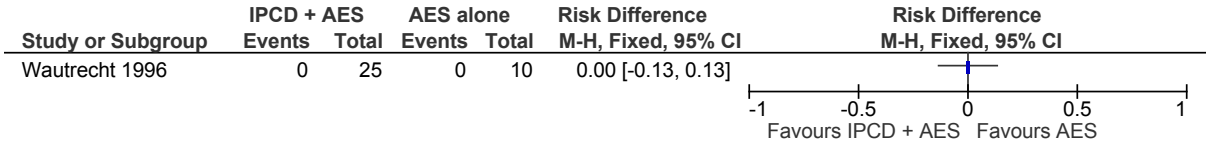
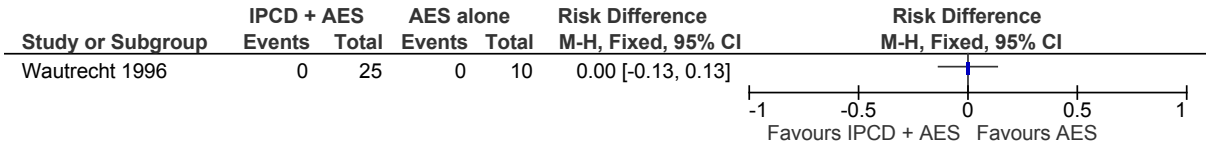


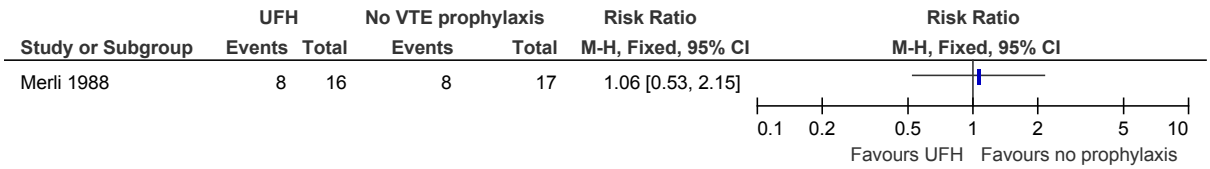
Figure 614: Fatal PE (8-10 days)



L.30 Spinal injury

L.30.1 UFH versus no VTE prophylaxis

Figure 615: DVT (28-42 days)



L.30.2 LMWH (standard dose; standard duration) versus no VTE prophylaxis

Figure 616: DVT (12-16 days)

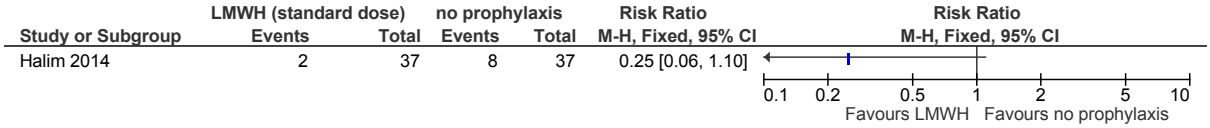


Figure 617: PE (12-16 days)

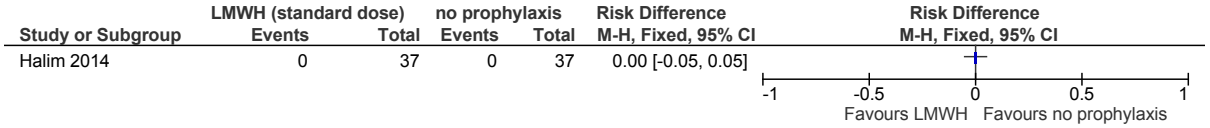
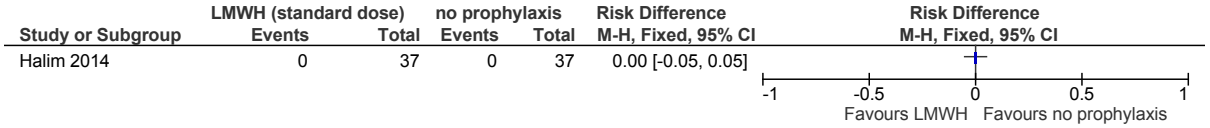


Figure 618: Fatal PE (12-16 days)



L.30.3 LMWH (standard dose; standard duration) versus UFH

Figure 619: All-cause mortality (56 days)

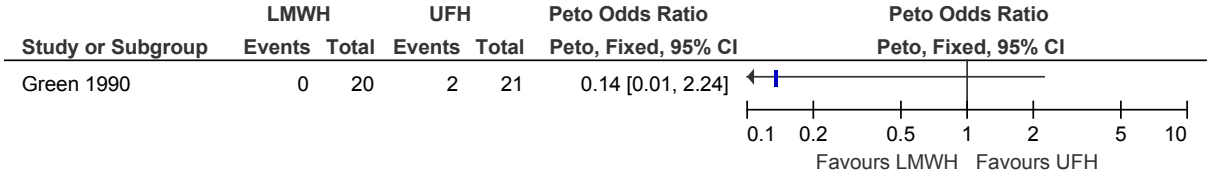


Figure 620: Fatal PE (56 days)

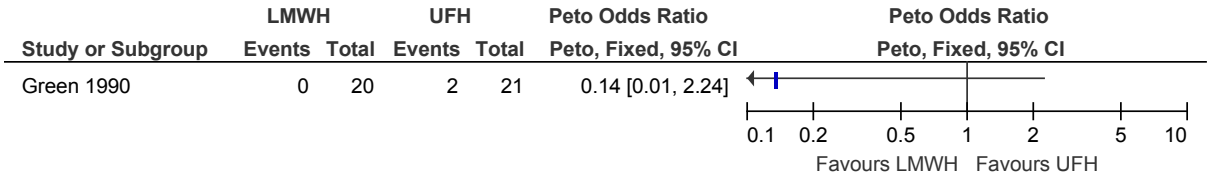


Figure 621: DVT (56 days)

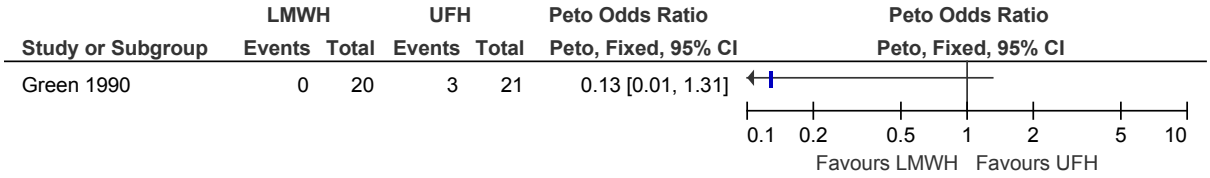
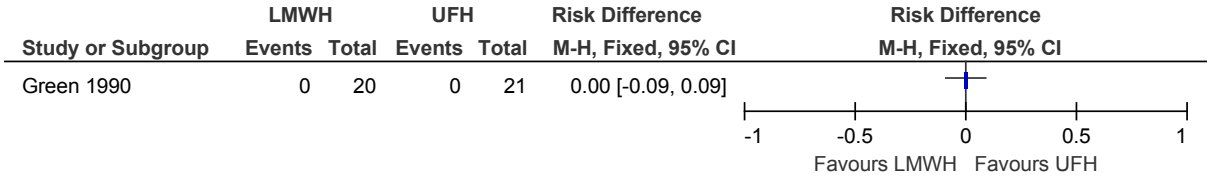


Figure 622: Major bleeding (56 days)



L.30.4 LMWH (high dose; standard duration) versus UFH+IPCD

Figure 623: All-cause mortality (56 days)

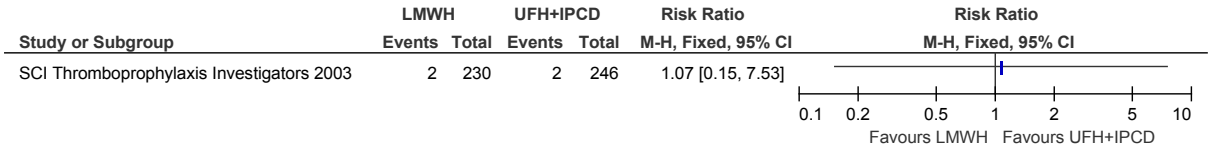


Figure 624: Fatal PE (56 days)

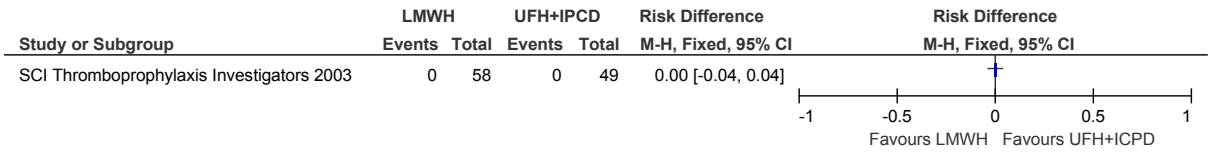


Figure 625: PE (56 days)

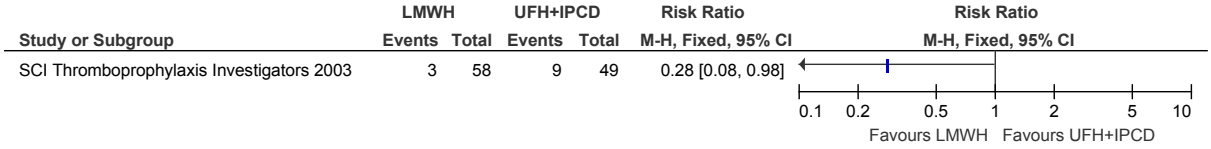


Figure 626: DVT (56 days)

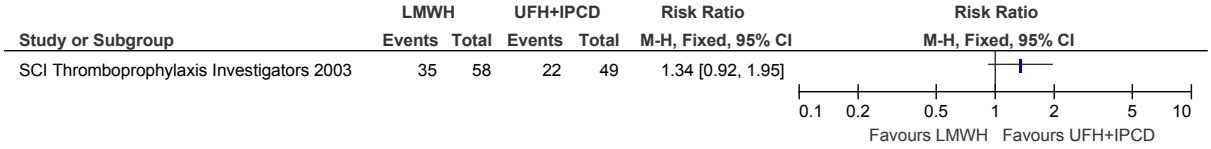
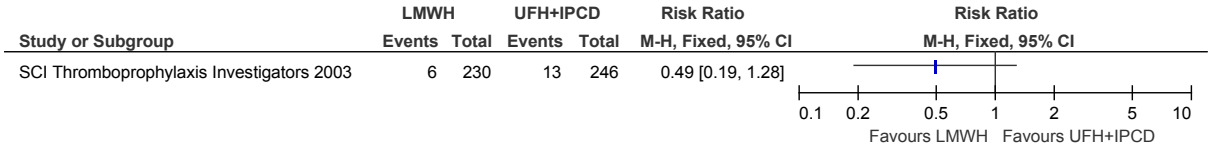


Figure 627: Major bleeding (56 weeks)



L.31 Major trauma

L.31.1 IPCD (full leg) versus no prophylaxis

Figure 628: **All-cause mortality (7-90 days)**

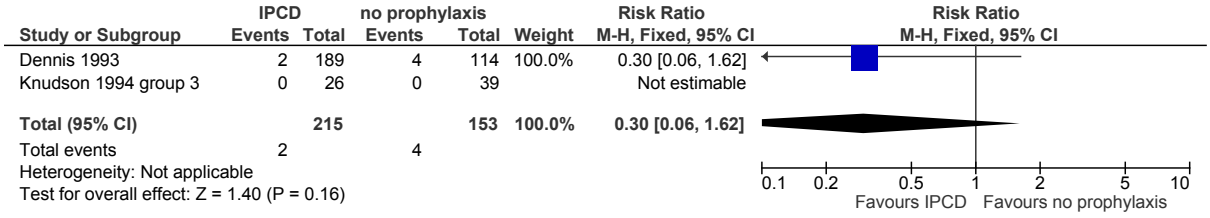


Figure 629: **DVT (symptomatic and asymptomatic) (7-90 days)**

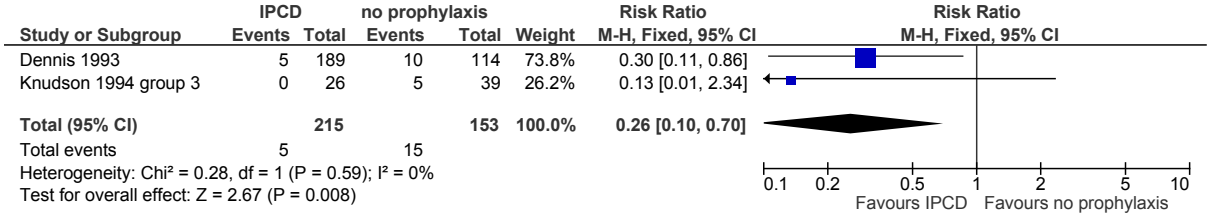


Figure 630: **PE (7-90 days)**

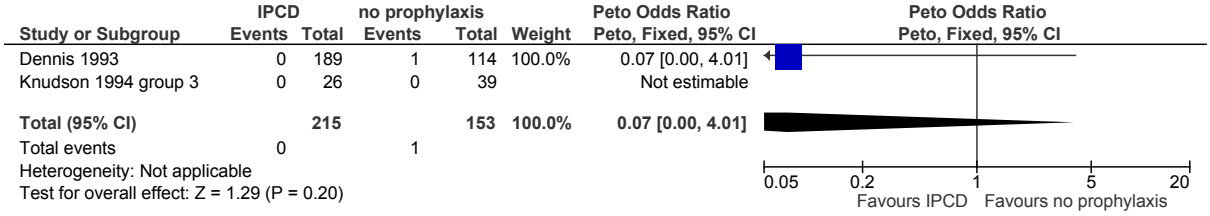
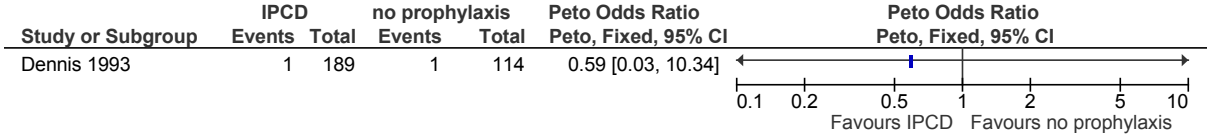


Figure 631: **Fatal PE (7-90 days)**



L.31.2 IPCD (full leg) versus foot pump

Figure 632: **All-cause mortality (time-point not reported)**

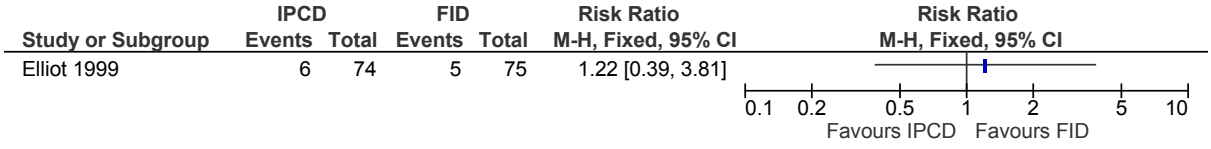


Figure 633: **DVT (symptomatic and asymptomatic) (time-point not reported)**

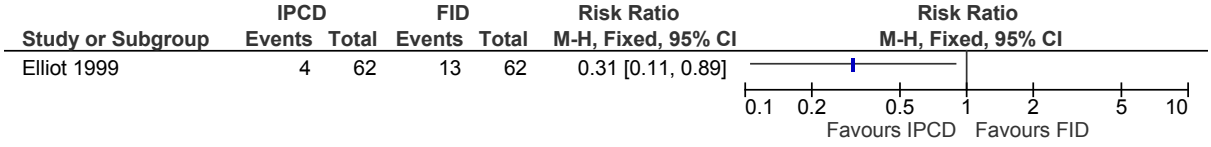
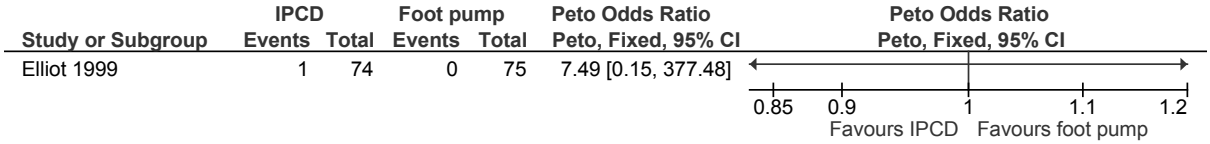


Figure 634: **Major bleeding (time-point not reported)**



L.31.3 IPCD (below knee) versus foot pump

Figure 635: **DVT (symptomatic and asymptomatic) (14 days)**

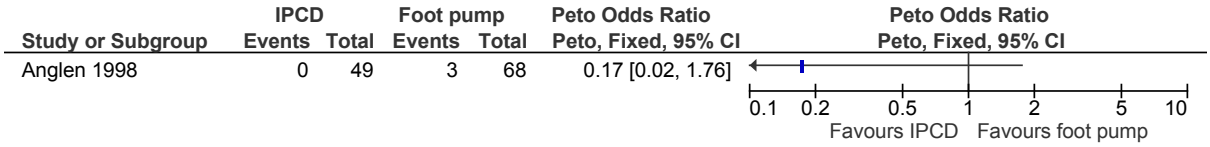
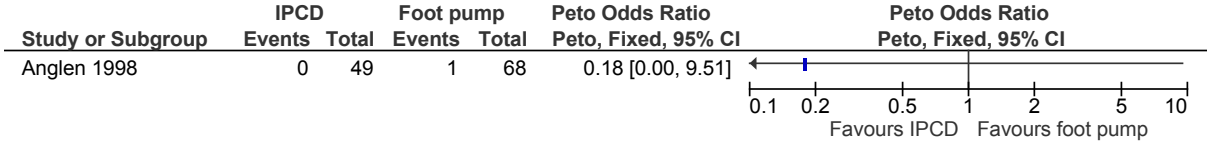


Figure 636: **PE (14 days)**



L.31.4 IPCD (full leg) + AES (length unspecified) versus no prophylaxis

Figure 637: **All-cause mortality (21 days)**

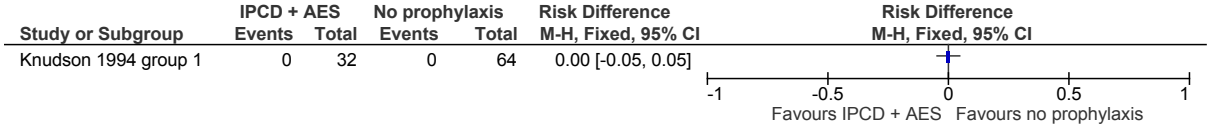


Figure 638: **DVT (symptomatic and asymptomatic) (21 days)**

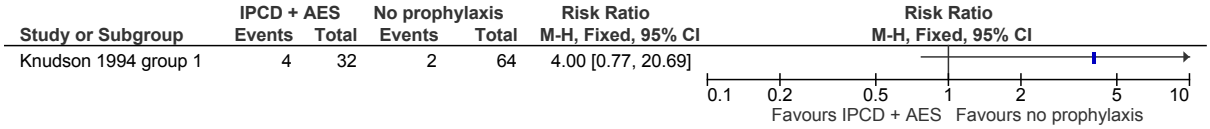
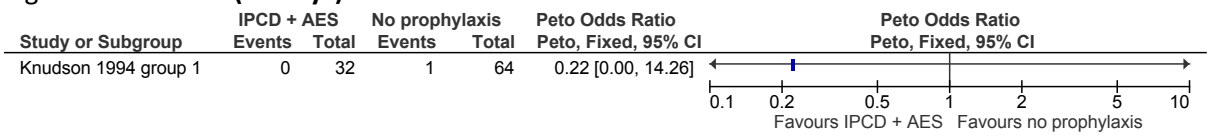


Figure 639: **PE (21 days)**



L.31.5 Continual passive motion + UFH versus UFH

Figure 640: **All-cause mortality (90 days)**

Study or Subgroup	Passive motion + UFH Events	Total	UFH Events	Total	Risk Difference M-H, Fixed, 95% CI
Fuchs 2005	0	111	0	116	0.00 [-0.02, 0.02]

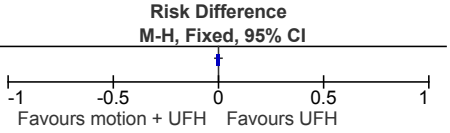


Figure 641: **DVT (symptomatic and asymptomatic) (90 days)**

Study or Subgroup	Passive motion + UFH Events	Total	UFH Events	Total	Risk Ratio M-H, Fixed, 95% CI
Fuchs 2005	4	111	29	116	0.14 [0.05, 0.40]

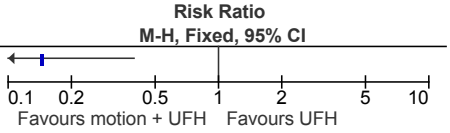
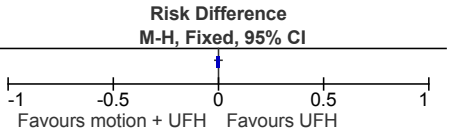


Figure 642: **PE (90 days)**

Study or Subgroup	Passive motion + UFH Events	Total	UFH Events	Total	Risk Difference M-H, Fixed, 95% CI
Fuchs 2005	0	111	0	116	0.00 [-0.02, 0.02]



L.31.6 UFH versus no prophylaxis

Figure 643: All-cause mortality (90 days)

Study or Subgroup	UFH Events	Total	No prophylaxis Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Dennis 1993	1	92	4	114	83.3%	0.36 [0.06, 2.14]
Knudson 1994 group 1	0	44	0	64		Not estimable
Knudson 1994 group 2	0	19	1	27	16.7%	0.18 [0.00, 9.75]
Total (95% CI)		**155**		**205**	**100.0%**	**0.32 [0.06, 1.64]**
Total events	1		5			

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)

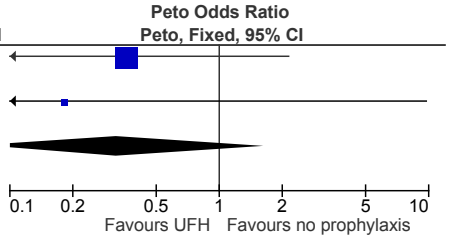


Figure 644: DVT (symptomatic and asymptomatic) (90 days)

Study or Subgroup	UFH Events	Total	No prophylaxis Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dennis 1993	3	92	10	114	73.1%	0.37 [0.11, 1.31]
Knudson 1994 group 1	1	44	2	64	13.3%	0.73 [0.07, 7.78]
Knudson 1994 group 2	1	19	2	27	13.5%	0.71 [0.07, 7.29]
Total (95% CI)		**155**		**205**	**100.0%**	**0.47 [0.17, 1.26]**
Total events	5		14			

Heterogeneity: Chi² = 0.39, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)

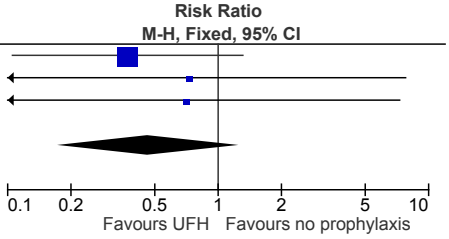


Figure 645: PE (90 days)

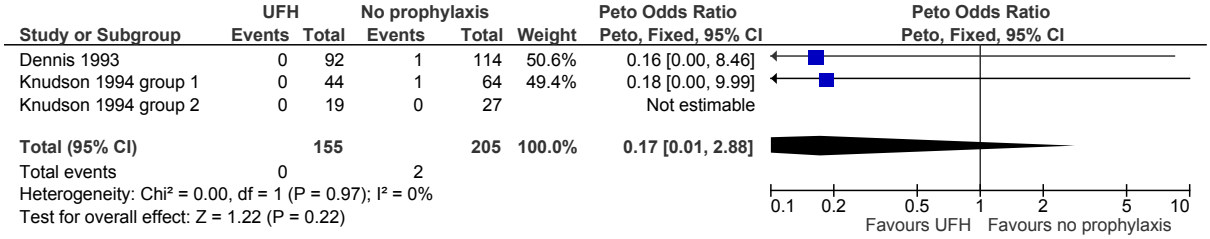
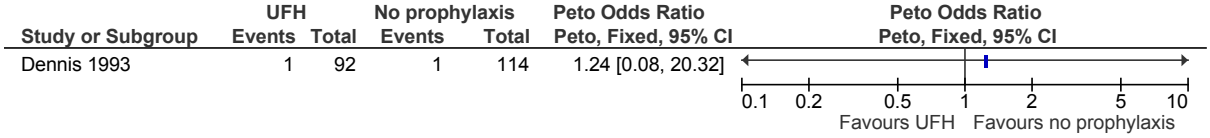


Figure 646: Fatal PE (90 days)



L.31.7 UFH versus IPCD (full leg)

Figure 647: **All-cause mortality (time-point not reported)**

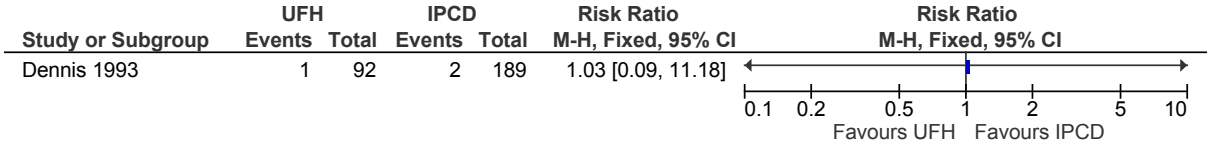


Figure 648: **DVT (symptomatic and asymptomatic) (time-point not reported)**

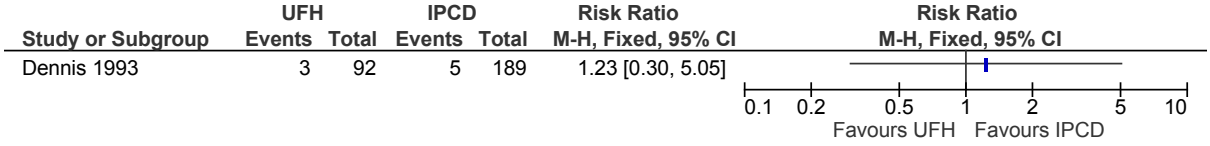


Figure 649: **PE (time-point not reported)**

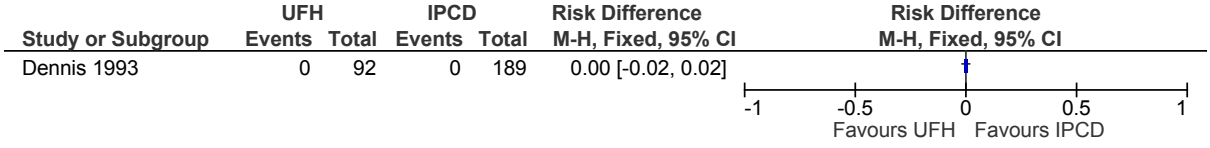
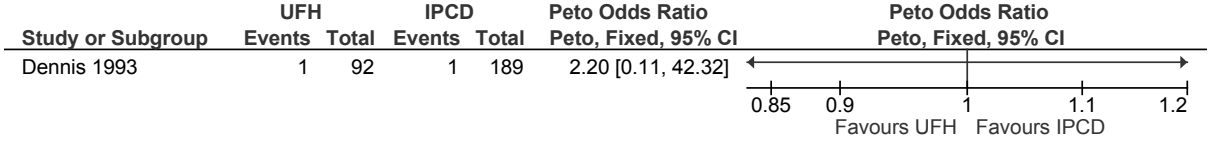


Figure 650: **Fatal PE (time-point not reported)**



L.31.8 UFH versus IPCD (full leg) + AES (undefined)

Figure 651: All-cause mortality (21 days)

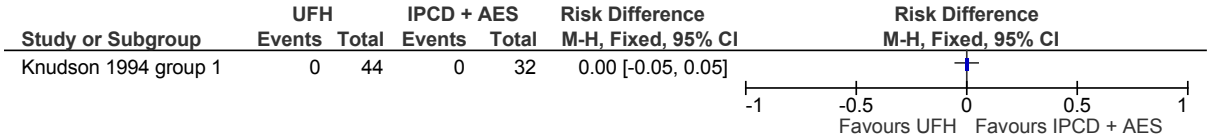


Figure 652: DVT (symptomatic and asymptomatic) (21 days)

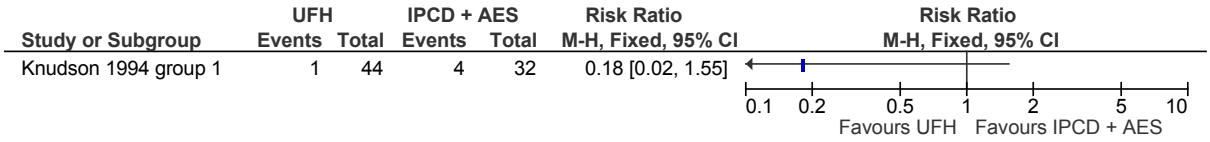
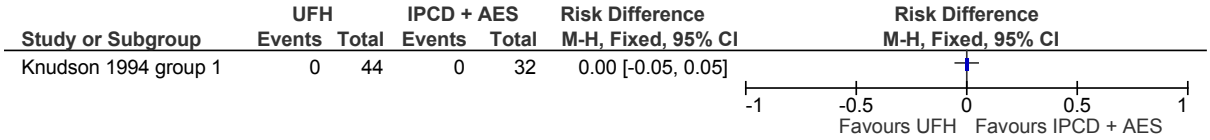


Figure 653: PE (21 days)



L.31.9 LMWH (standard dose; standard duration) + IPCD (below knee) versus IPCD (below knee)

Figure 654: **All-cause mortality (time-point not reported)**

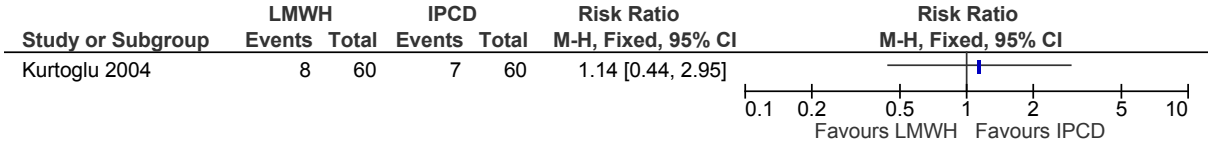


Figure 655: **DVT (symptomatic and asymptomatic) (time-point not reported)**

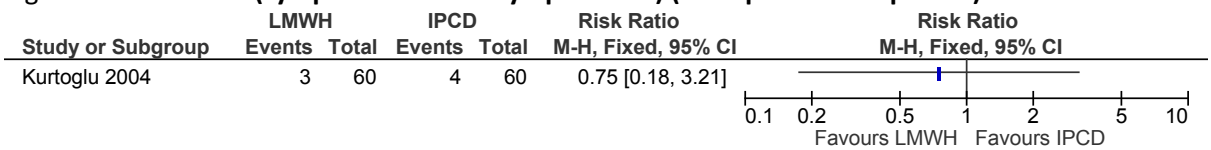


Figure 656: **PE (time-point not reported)**

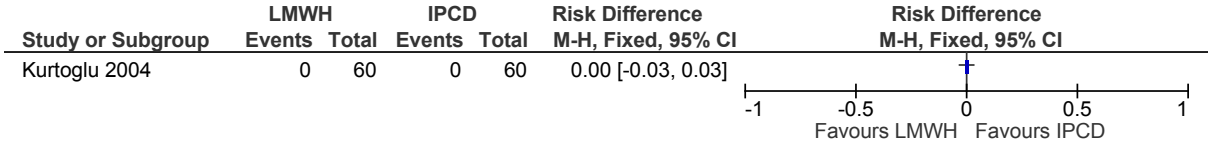


Figure 657: **Major bleeding (time-point not reported)**

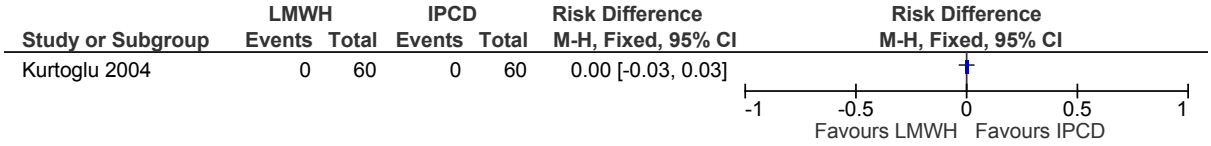
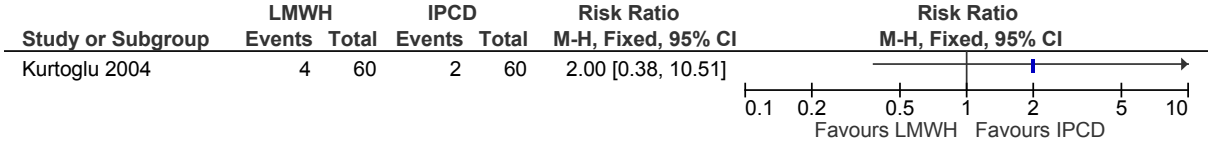


Figure 658: **Fatal PE (time-point not reported)**



L.31.10 LMWH (high dose; standard duration) versus UFH

Figure 659: All-cause mortality (14 days)

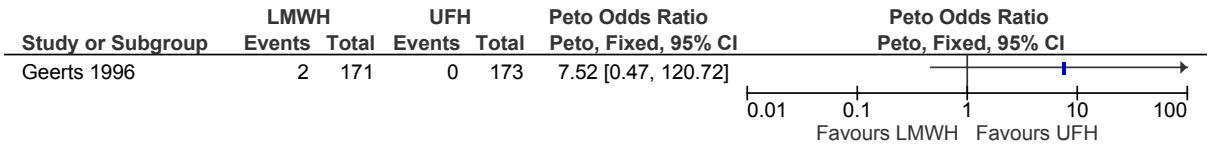


Figure 660: DVT (symptomatic and asymptomatic) (10-14 days)

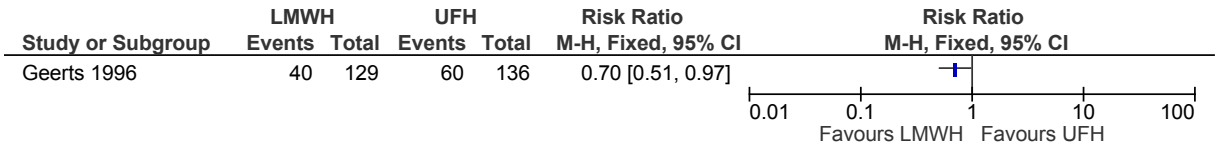


Figure 661: PE (14 days)

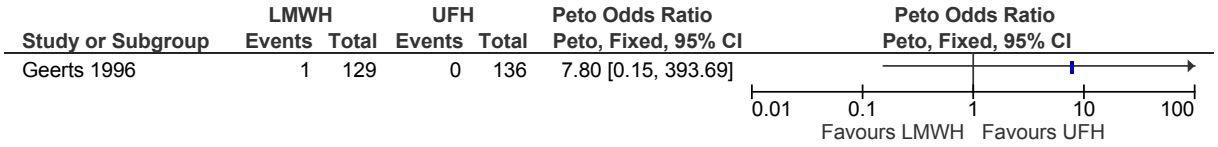


Figure 662: Major bleeding (14 days)

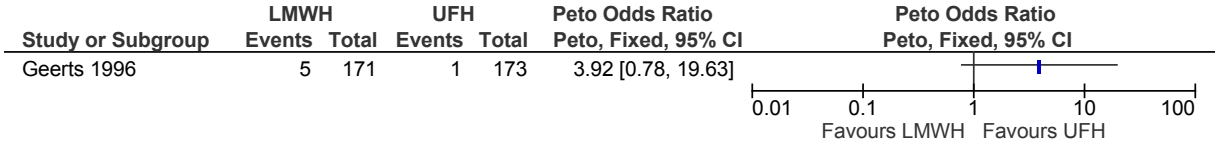
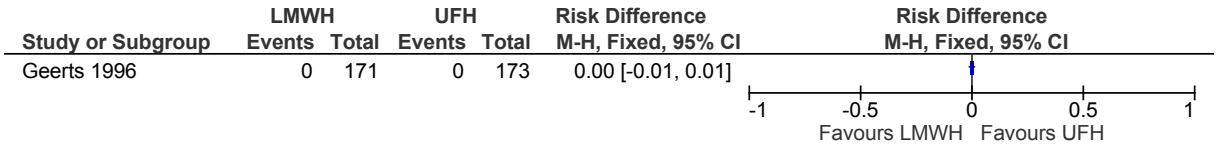


Figure 663: Fatal PE (14 days)



L.31.11 LMWH (high dose; standard duration) versus IPCD (below knee)

Figure 664: All-cause mortality (30 days)

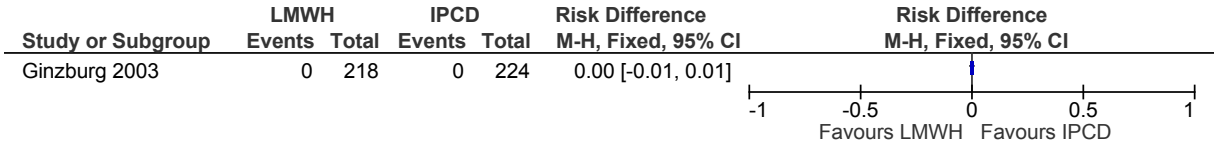


Figure 665: DVT (symptomatic and asymptomatic) (30 days)

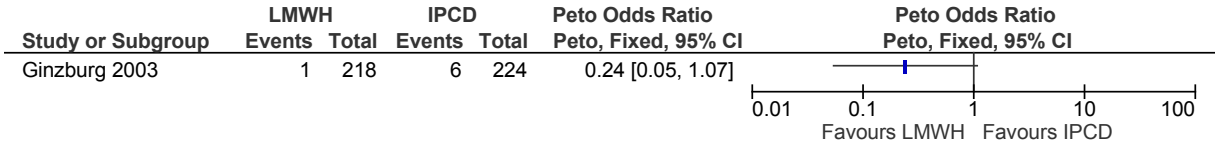


Figure 666: PE (30 days)

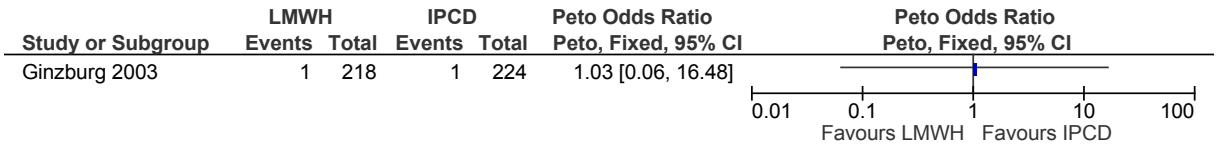
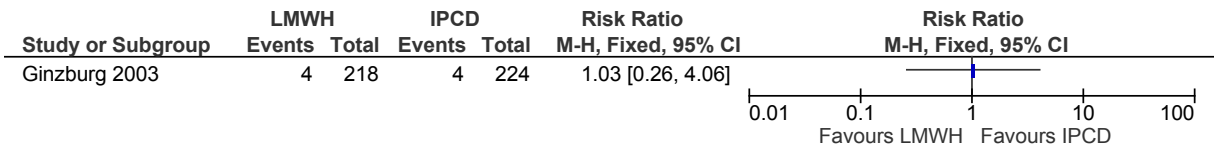


Figure 667: Major bleeding (30 days)



L.31.12 LMWH (high dose; standard duration) versus (IPCD, undefined + AES, undefined) or FID

Figure 668: All-cause mortality (time-point not reported)

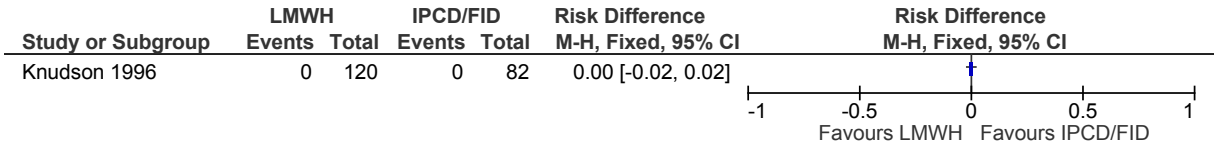


Figure 669: DVT (time point not reported)

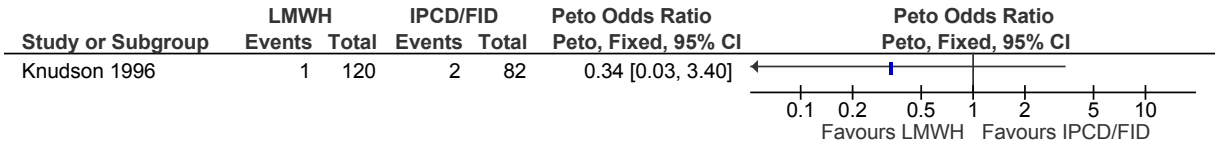
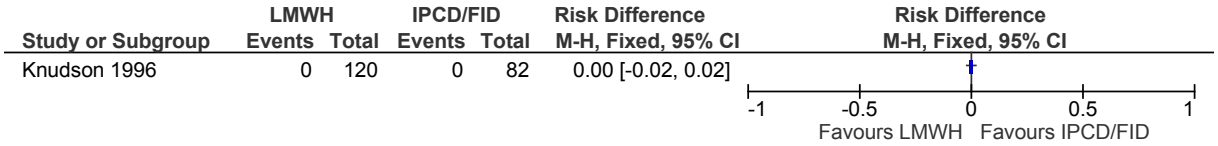


Figure 670: PE (time point not reported)



L.31.13 LMWH (high dose; standard duration) versus delayed LMWH (high dose; standard duration) + foot pump

Figure 671: All-cause mortality (time point not reported)

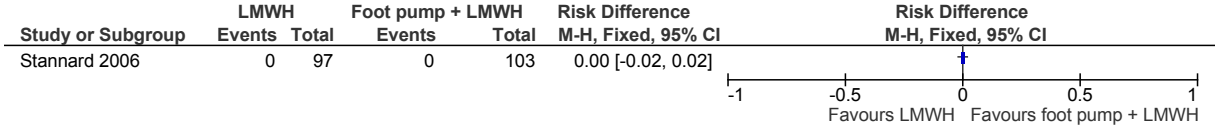


Figure 672: DVT (time point not reported)

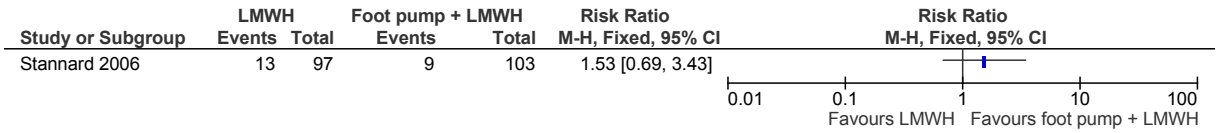


Figure 673: PE (time point not reported)

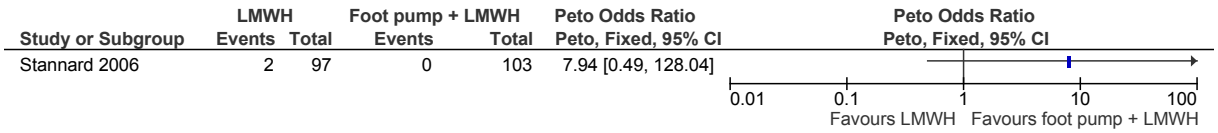
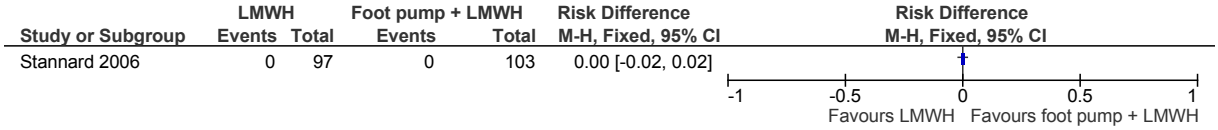


Figure 674: Fatal PE (time point not reported)



L.32 Abdominal surgery (excluding bariatric surgery)

L.32.1 AES (above knee) versus no prophylaxis

Figure 675: All-cause mortality (time-point not reported)

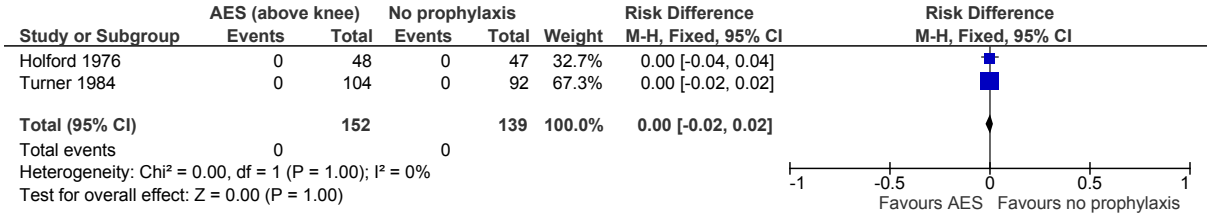


Figure 676: DVT (symptomatic and asymptomatic) (time-point not reported)

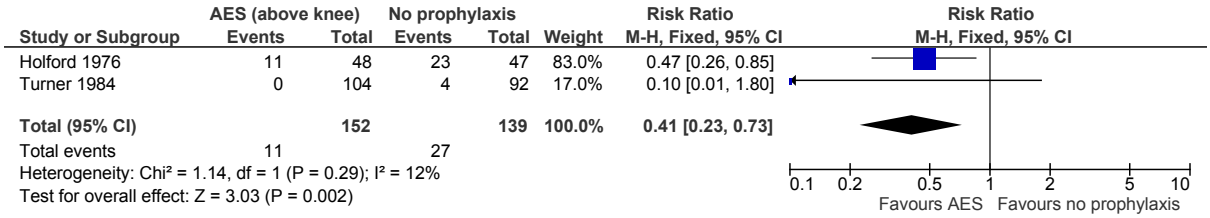
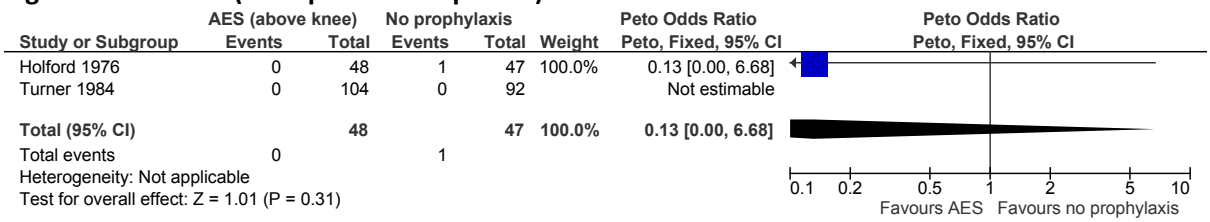
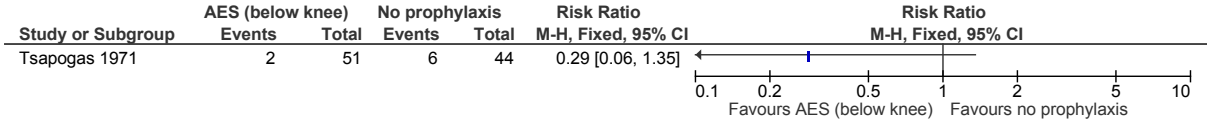


Figure 677: PE (time-point not reported)



L.32.2 AES (below knee) versus no prophylaxis

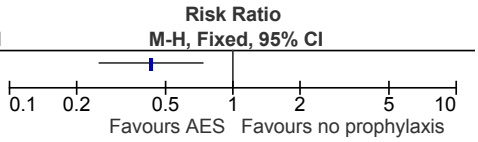
Figure 678: DVT (symptomatic and asymptomatic) (7 days)



L.32.3 AES (undefined) versus no prophylaxis

Figure 679: DVT (symptomatic and asymptomatic) (7 days)

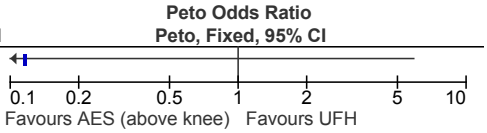
Study or Subgroup	AES Events	AES Total	No prophylaxis Events	No prophylaxis Total	Risk Ratio M-H, Fixed, 95% CI
Allan 1983	15	97	37	103	0.43 [0.25, 0.73]



L.32.4 AES (above knee) versus UFH

Figure 680: Fatal PE (time-point not reported)

Study or Subgroup	AES (above knee) Events	AES (above knee) Total	UFH Events	UFH Total	Peto Odds Ratio Peto, Fixed, 95% CI
Fasting 1985	0	52	1	45	0.12 [0.00, 5.90]



L.32.5 AES (below knee) versus UFH

Figure 681: All-cause mortality (time-point not reported)

Study or Subgroup	AES (below knee) Events	AES (below knee) Total	UFH Events	UFH Total	Risk Difference M-H, Fixed, 95% CI
Rasmussen 1988	0	74	0	85	0.00 [-0.02, 0.02]

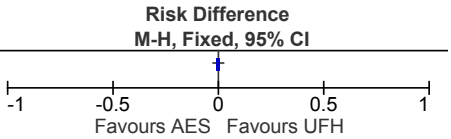
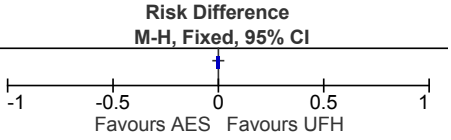


Figure 682: PE (time-point not reported)

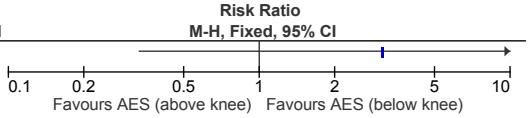
Study or Subgroup	AES (below knee) Events	AES (below knee) Total	UFH Events	UFH Total	Risk Difference M-H, Fixed, 95% CI
Rasmussen 1988	0	74	0	85	0.00 [-0.02, 0.02]



L.32.6 AES (above knee) versus AES (below knee)

Figure 683: DVT (symptomatic and asymptomatic) (time-point not reported)

Study or Subgroup	AES (above knee) Events	AES (above knee) Total	AES (below knee) Events	AES (below knee) Total	Risk Ratio M-H, Fixed, 95% CI
Porteous 1989	3	56	1	58	3.11 [0.33, 28.99]



L.32.7 AES (below knee) + UFH versus AES (below knee)

Figure 684: All-cause mortality (time-point not reported)

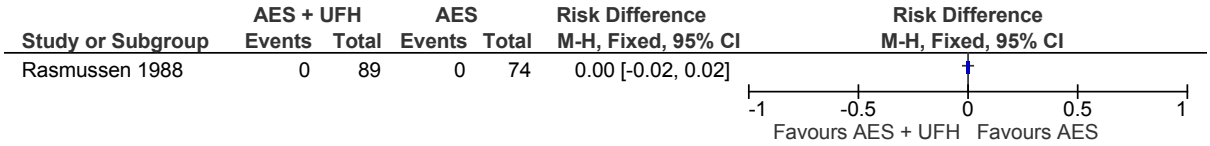
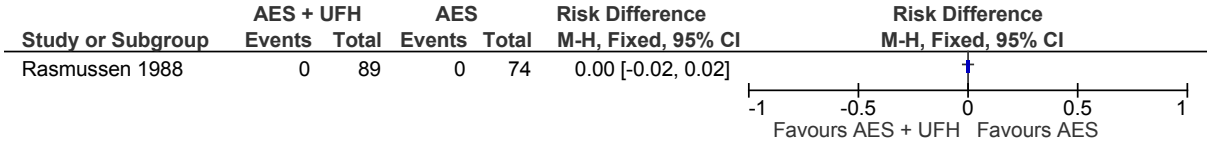


Figure 685: PE (time-point not reported)



L.32.8 AES (above knee) + UFH versus UFH

Figure 686: All-cause mortality (30 days)

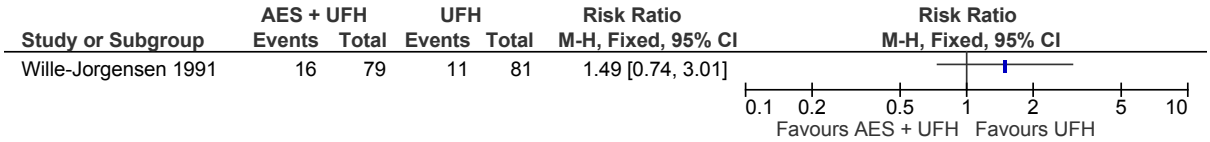


Figure 687: DVT (symptomatic and asymptomatic) (30 days)

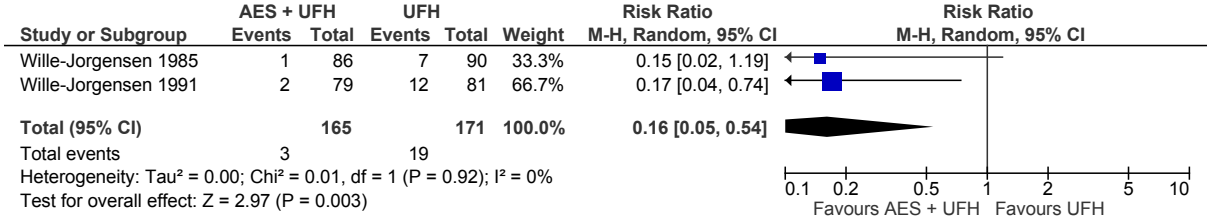


Figure 688: PE (30 days)

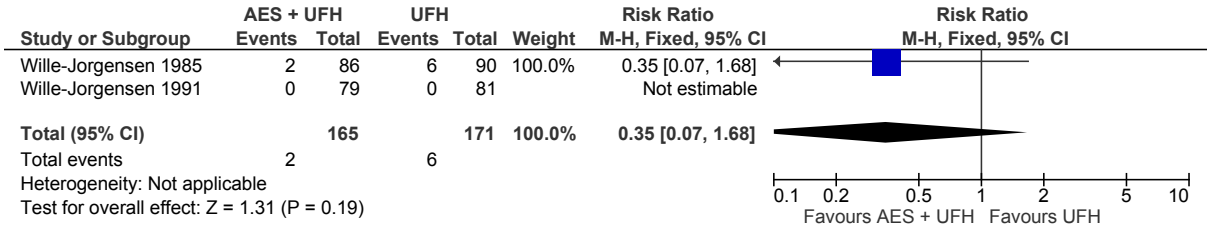
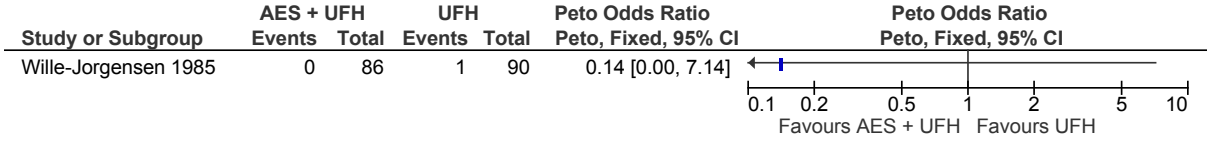


Figure 689: Fatal PE (30 days)



L.32.9 AES (below knee) + UFH versus UFH

Figure 690: All-cause mortality (time-point not reported)

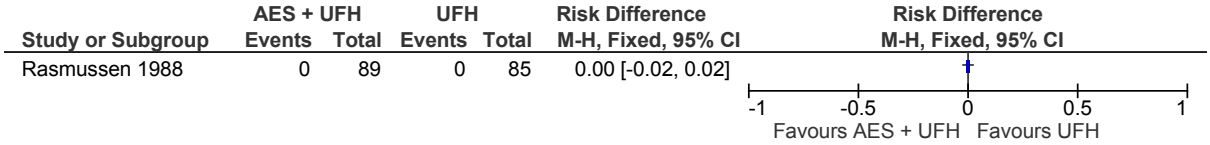
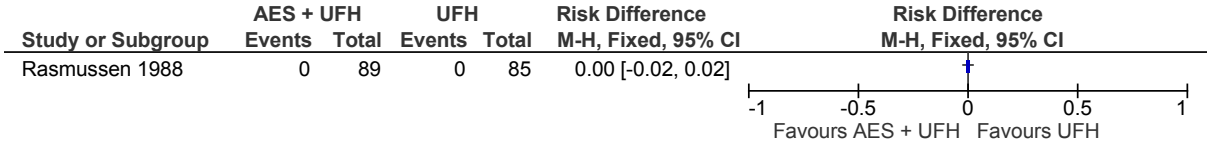


Figure 691: PE (time-point not reported)



L.32.10 AES (above knee) + IPCD (full leg) versus AES (above knee)

Figure 692: DVT (symptomatic and asymptomatic) (time-point not reported)

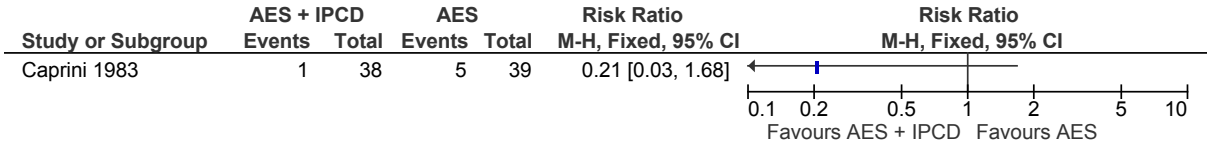


Figure 693: PE (time-point not reported)

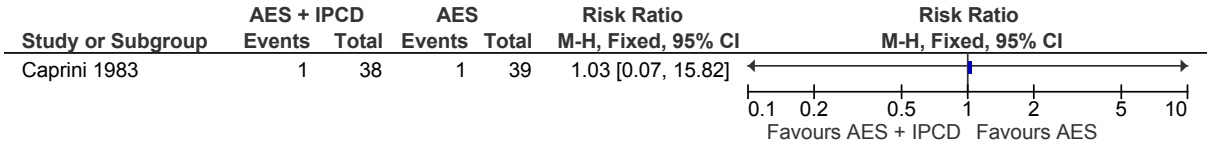
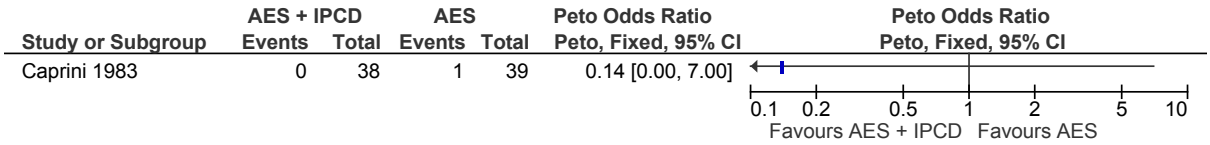


Figure 694: Fatal PE (time-point not reported)



L.32.11 AES (undefined) + IPCD (full leg) versus AES (undefined)

Figure 695: DVT (symptomatic and asymptomatic) (time-point not reported)

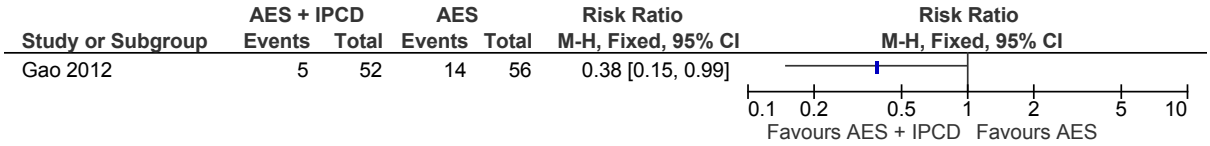
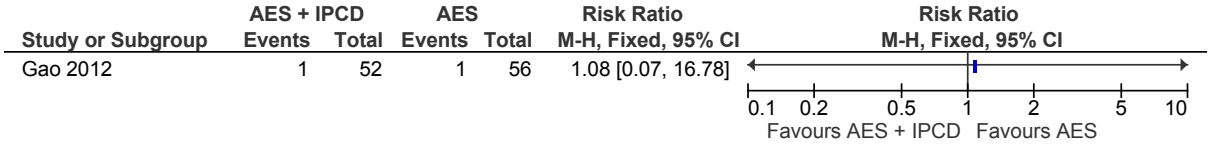
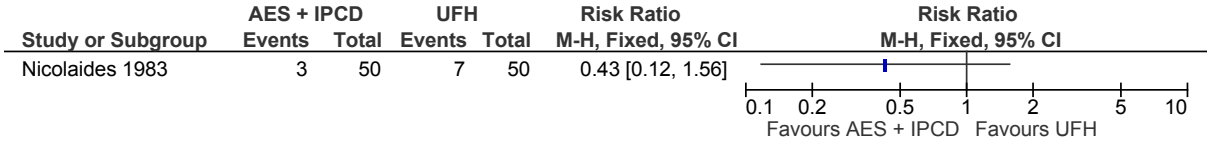


Figure 696: PE (time-point not reported)



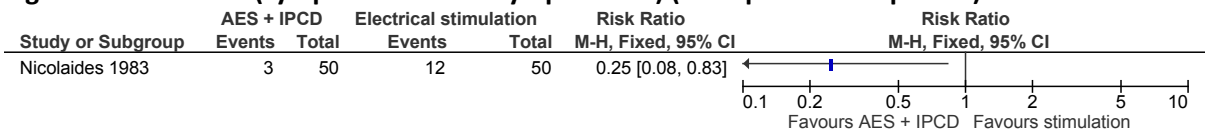
L.32.12 AES (undefined) + IPCD (full leg) versus UFH

Figure 697: DVT (symptomatic and asymptomatic) (time-point not reported)



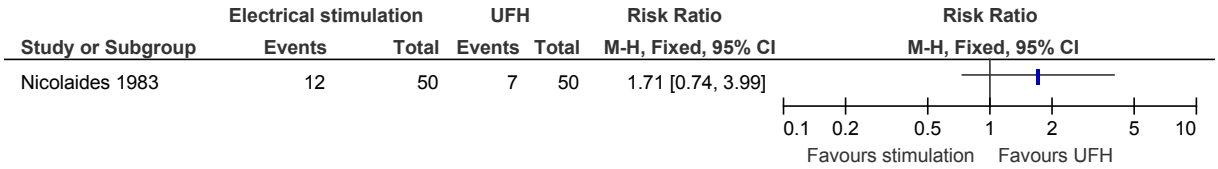
L.32.13 AES (undefined) + IPCD (full leg) versus electrical stimulation

Figure 698: DVT (symptomatic and asymptomatic) (time-point not reported)



L.32.14 Electrical stimulation versus UFH

Figure 699: DVT (symptomatic and asymptomatic) (time-point not reported)



L.32.15 Foot pump versus no prophylaxis

Figure 700: All-cause mortality (7 days)

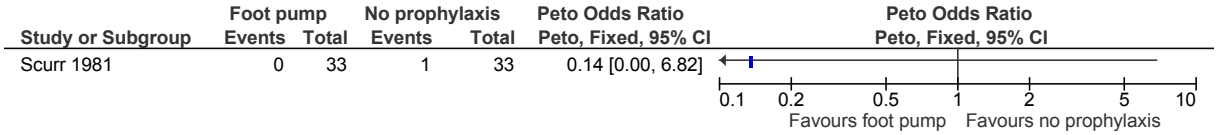
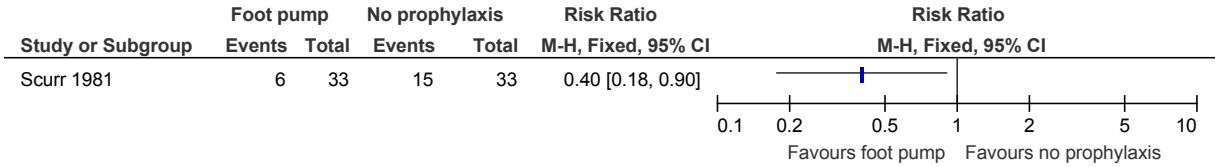


Figure 701: DVT (symptomatic and asymptomatic) (7 days)



L.32.16 FID + IPCD (below knee) + LMWH (standard dose) versus FID + IPCD (below knee)

Figure 702: DVT (symptomatic and asymptomatic) (11 days)

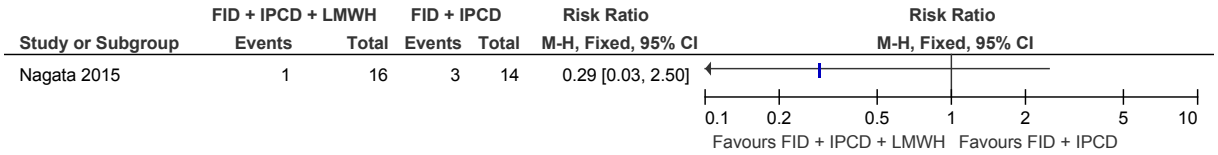


Figure 703: PE (11 days)

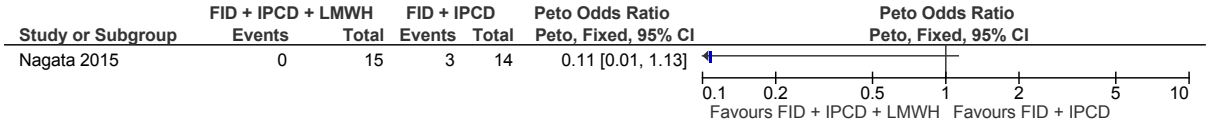
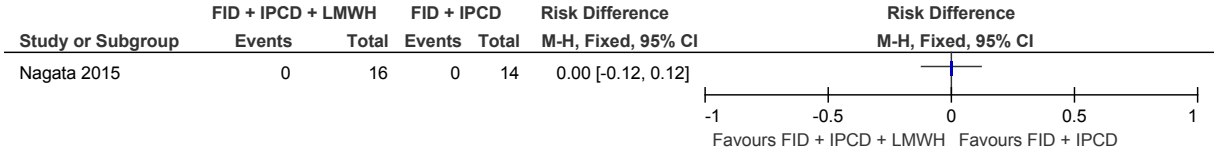


Figure 704: Thrombocytopenia (6 days)



L.32.17 IPCD (below knee) versus no prophylaxis

Figure 705: All-cause mortality (42 days)

Study or Subgroup	IPCD Events	IPCD Total	No prophylaxis Events	No prophylaxis Total	Risk Difference M-H, Fixed, 95% CI
Clarke-Pearson 1984B	0	55	0	52	0.00 [-0.04, 0.04]

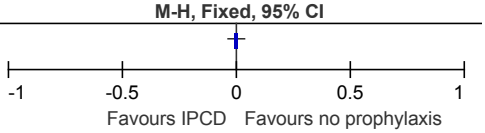


Figure 706: DVT (symptomatic and asymptomatic) (90 days)

Study or Subgroup	IPCD Events	IPCD Total	No prophylaxis Events	No prophylaxis Total	Weight	Risk Ratio M-H, Random, 95% CI
Butson 1981	6	62	4	57	22.9%	1.38 [0.41, 4.64]
Clarke-Pearson 1984A	14	97	11	97	30.7%	1.27 [0.61, 2.66]
Clarke-Pearson 1984B	5	55	17	52	27.6%	0.28 [0.11, 0.70]
Coe 1978	2	29	6	24	18.8%	0.28 [0.06, 1.24]
Total (95% CI)		**243**		**230**	**100.0%**	**0.64 [0.26, 1.59]**
Total events	27		38			

Heterogeneity: Tau² = 0.56; Chi² = 9.08, df = 3 (P = 0.03); I² = 67%
Test for overall effect: Z = 0.96 (P = 0.34)

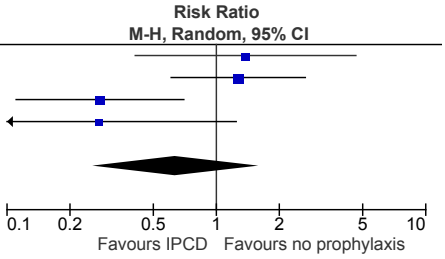


Figure 707: PE (42 days)

Study or Subgroup	IPCD Events	IPCD Total	No prophylaxis Events	No prophylaxis Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Clarke-Pearson 1984A	4	97	1	97	32.0%	4.00 [0.46, 35.14]
Clarke-Pearson 1984B	2	55	1	52	32.9%	1.89 [0.18, 20.23]
Coe 1978	1	29	1	24	35.0%	0.83 [0.05, 12.54]
Total (95% CI)		**181**		**173**	**100.0%**	**2.19 [0.58, 8.24]**
Total events	7		3			

Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.24)

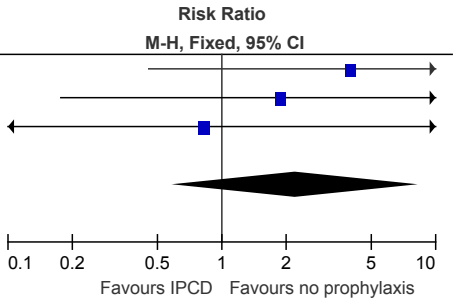
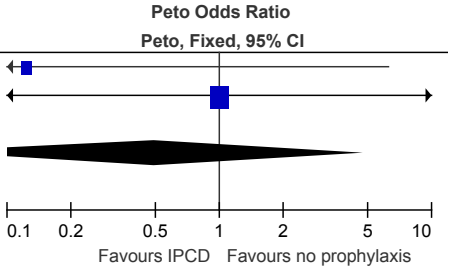


Figure 708: Fatal PE (90 days)

Study or Subgroup	IPCD Events	IPCD Total	No prophylaxis Events	No prophylaxis Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Butson 1981	0	62	1	57	33.4%	0.12 [0.00, 6.27]
Clarke-Pearson 1984A	1	97	1	97	66.6%	1.00 [0.06, 16.10]
Total (95% CI)		**159**		**154**	**100.0%**	**0.50 [0.05, 4.81]**
Total events	1		2			

Heterogeneity: Chi² = 0.72, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)



L.32.18 IPCD (full leg) versus IPCD (below knee)

Figure 709: DVT (symptomatic and asymptomatic) (90 days)

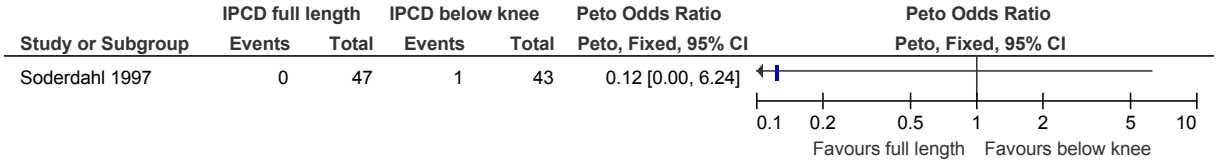


Figure 710: PE (90 days)

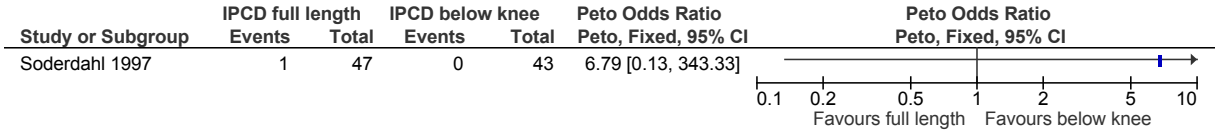
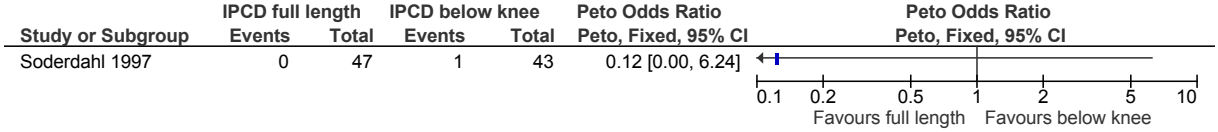


Figure 711: Fatal PE (90 days)



L.32.19 IPCD (full leg) versus VKA

Figure 712: All-cause mortality (7-14 days)

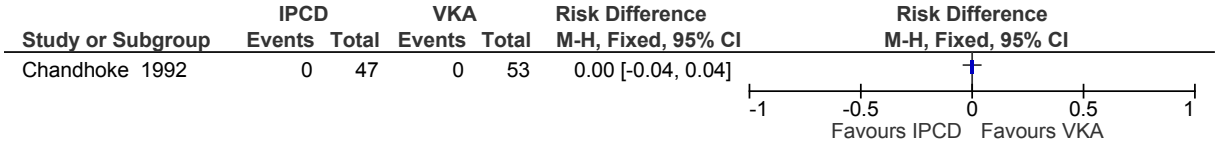


Figure 713: DVT (symptomatic and asymptomatic) (7-14 days)

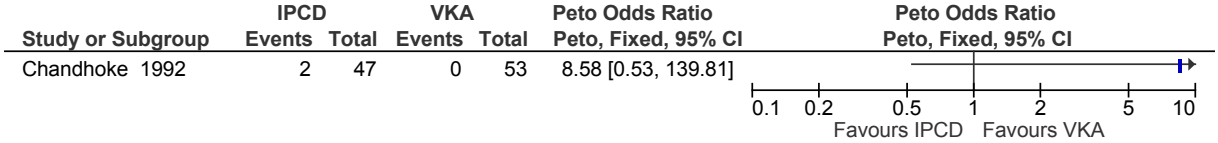
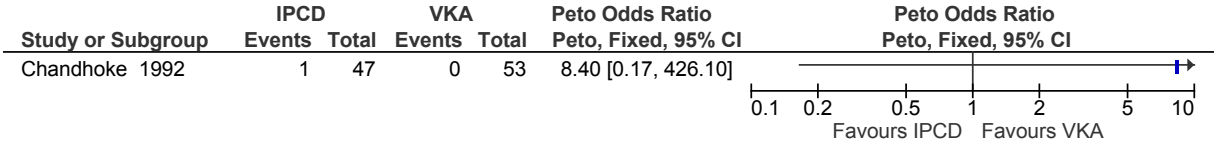


Figure 714: PE (7-14 days)



L.32.20 IPCD (undefined) + LMWH (standard dose) versus IPCD (undefined)

Figure 715: DVT (symptomatic and asymptomatic) (14-30 days)

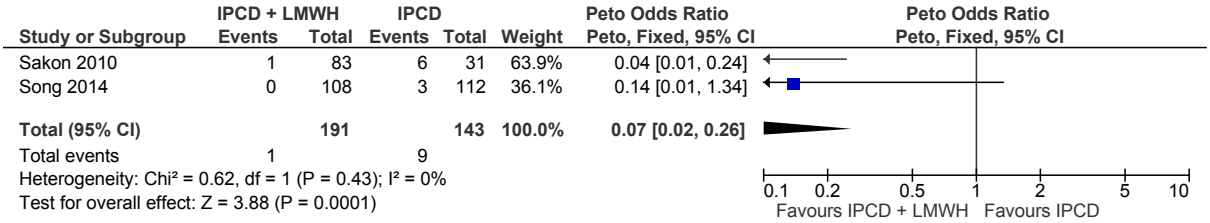
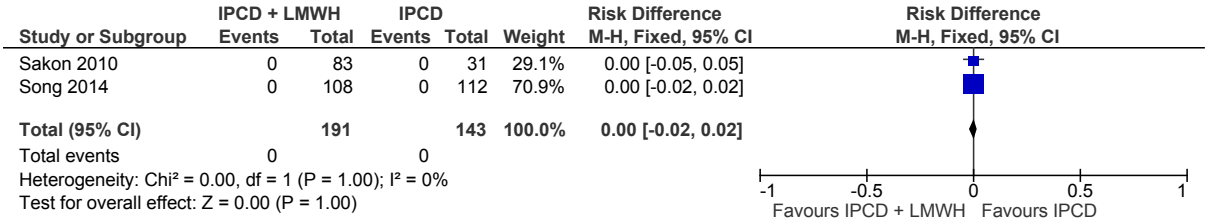


Figure 716: PE (14-30 days)



L.32.21 UFH versus no prophylaxis/mechanical

Figure 717: All-cause mortality (5-8 days)

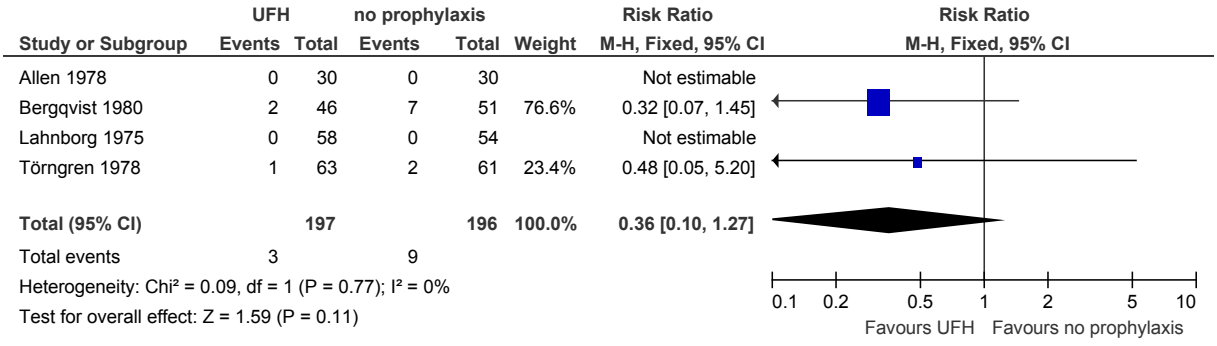


Figure 718: DVT (symptomatic and asymptomatic) (7-70 days)

Study or Subgroup	UFH Events	UFH Total	no prophylaxis Events	no prophylaxis Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bergqvist 1980	6	46	14	51	9.7%	0.48 [0.20, 1.13]
Clarke-Pearson 1983	11	88	11	97	7.6%	1.10 [0.50, 2.42]
Coe 1978	6	28	6	24	4.7%	0.86 [0.32, 2.31]
Gallus 1973	1	108	4	118	2.8%	0.27 [0.03, 2.41]
Gallus 1976	4	408	12	412	8.7%	0.34 [0.11, 1.04]
Gordon-Smith 1972	4	48	21	50	15.0%	0.20 [0.07, 0.54]
Kakkar 1972	3	39	17	39	12.4%	0.18 [0.06, 0.55]
Osman 2007	0	25	0	25		Not estimable
Strand 1975	3	50	10	50	7.3%	0.30 [0.09, 1.03]
Taberner 1978	3	49	11	48	8.1%	0.27 [0.08, 0.90]
Törngren 1978	10	63	20	61	14.8%	0.48 [0.25, 0.95]
Vandendris 1980	3	31	13	33	9.2%	0.25 [0.08, 0.78]
Total (95% CI)		**983**		**1008**	**100.0%**	**0.40 [0.30, 0.53]**
Total events	54		139			

Heterogeneity: Chi² = 14.62, df = 10 (P = 0.15); I² = 32%
Test for overall effect: Z = 6.23 (P < 0.00001)

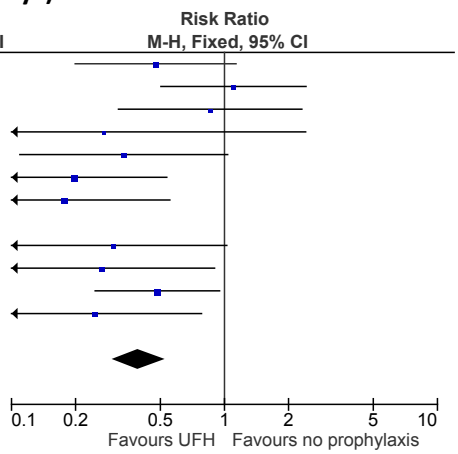


Figure 719: PE (7-70 days)

Study or Subgroup	UFH Events	UFH Total	no prophylaxis Events	no prophylaxis Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bejjani 1983	0	17	1	17	5.0%	0.33 [0.01, 7.65]
Clarke-Pearson 1983	4	88	0	97	1.6%	9.91 [0.54, 181.48]
Coe 1978	1	28	1	24	3.6%	0.86 [0.06, 12.98]
Gordon-Smith 1972	0	52	0	50		Not estimable
Kakkar 1972	0	39	0	39		Not estimable
Lahnborg 1975	9	58	24	54	83.0%	0.35 [0.18, 0.68]
Osman 2007	0	25	0	25		Not estimable
Strand 1975	0	50	0	50		Not estimable
Törngren 1978	1	63	2	61	6.8%	0.48 [0.05, 5.20]
Vandendris 1980	0	31	0	33		Not estimable
Total (95% CI)		**451**		**450**	**100.0%**	**0.53 [0.31, 0.91]**
Total events	15		28			

Heterogeneity: Chi² = 5.58, df = 4 (P = 0.23); I² = 28%
Test for overall effect: Z = 2.29 (P = 0.02)

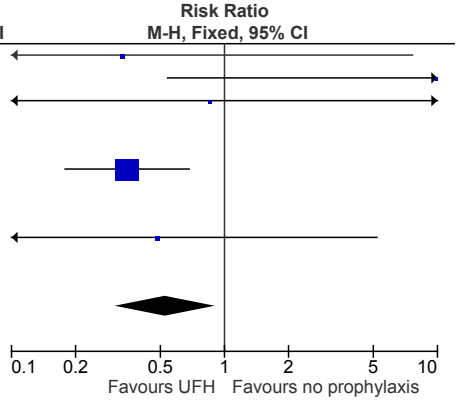


Figure 720: Major bleeding (6-14 days)

Study or Subgroup	UFH Events	UFH Total	no prophylaxis Events	no prophylaxis Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Allen 1978	6	30	0	30	2.1%	13.00 [0.76, 220.96]
Bejjani 1983	1	17	0	17	2.1%	3.00 [0.13, 68.84]
Fasting 1985	0	52	0	45		Not estimable
Lahnborg 1975	0	58	0	54		Not estimable
Osman 2007	0	25	0	25		Not estimable
Rasmussen 1988	0	174	0	74		Not estimable
Törngren 1978	24	63	23	61	95.9%	1.01 [0.64, 1.59]
Total (95% CI)		**419**		**306**	**100.0%**	**1.30 [0.84, 2.00]**
Total events	31		23			

Heterogeneity: Chi² = 4.00, df = 2 (P = 0.14); I² = 50%
Test for overall effect: Z = 1.17 (P = 0.24)

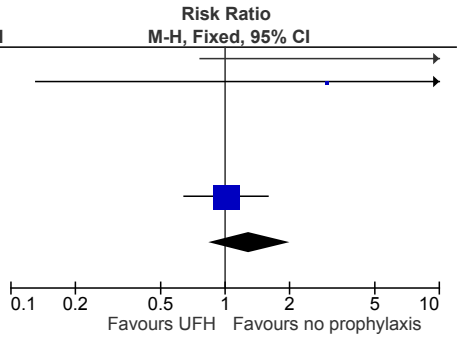
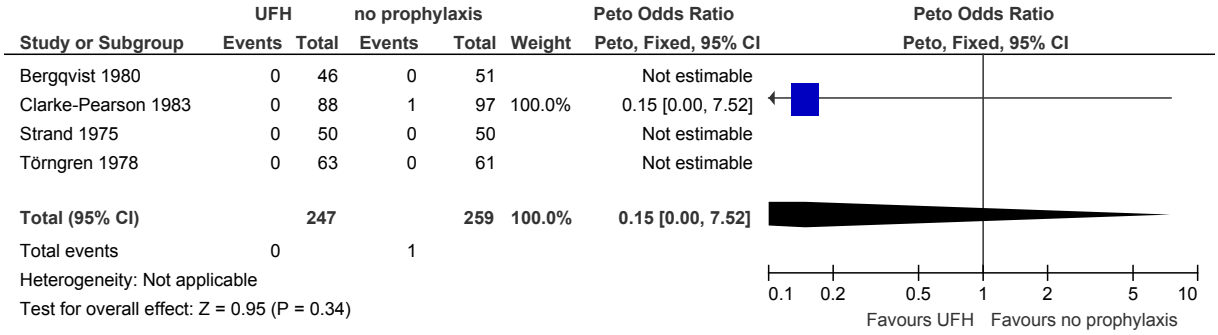


Figure 721: Fatal PE (7-90 days)



L.32.22 UFH versus IPCD (below knee)

Figure 722: DVT (symptomatic and asymptomatic) (30 days)

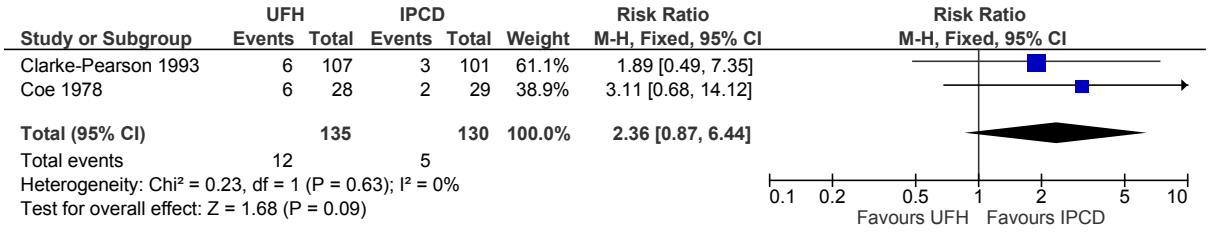
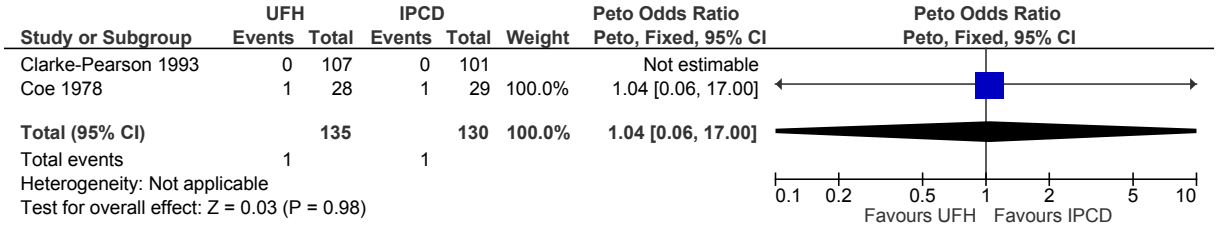


Figure 723: PE (30 days)



L.32.23 UFH versus VKA

Figure 724: DVT (symptomatic and asymptomatic) (time-point not reported)

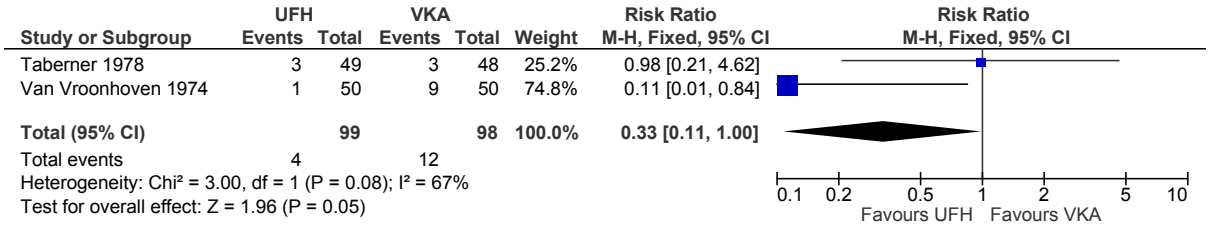
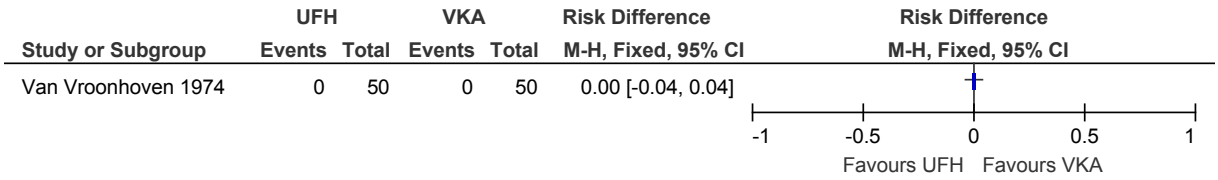


Figure 725: Major bleeding (time-point not reported)



L.32.24 LMWH (low dose; standard duration) versus no prophylaxis

Figure 726: All-cause mortality (42 days)

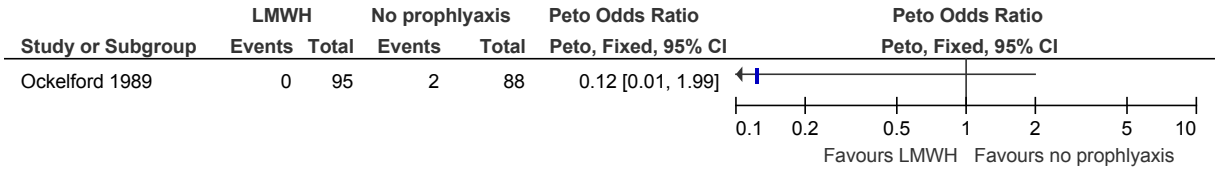


Figure 727: DVT (symptomatic and asymptomatic) (42 days)

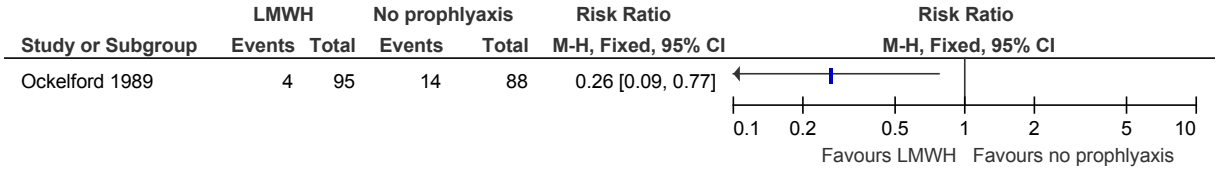


Figure 728: PE (42 days)

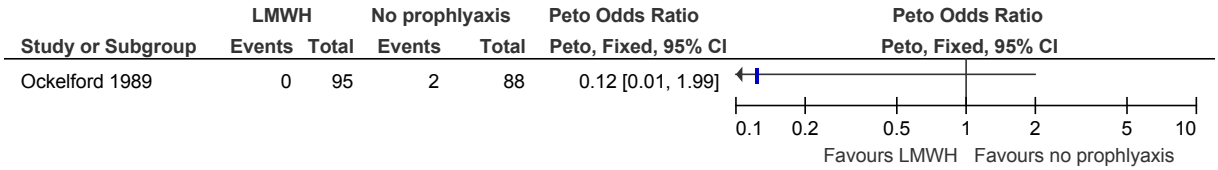


Figure 729: Major bleeding (42 days)

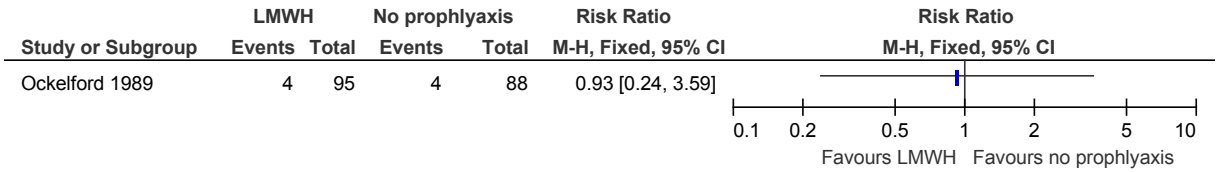
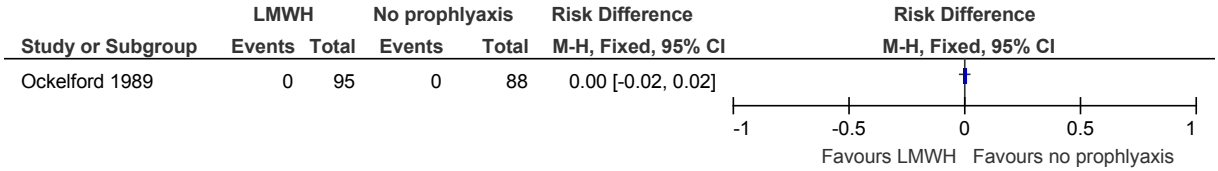


Figure 730: Thrombocytopenia (42 days)



L.32.25 LMWH (low dose; standard duration) versus UFH

Figure 731: All-cause mortality (6-56 days)

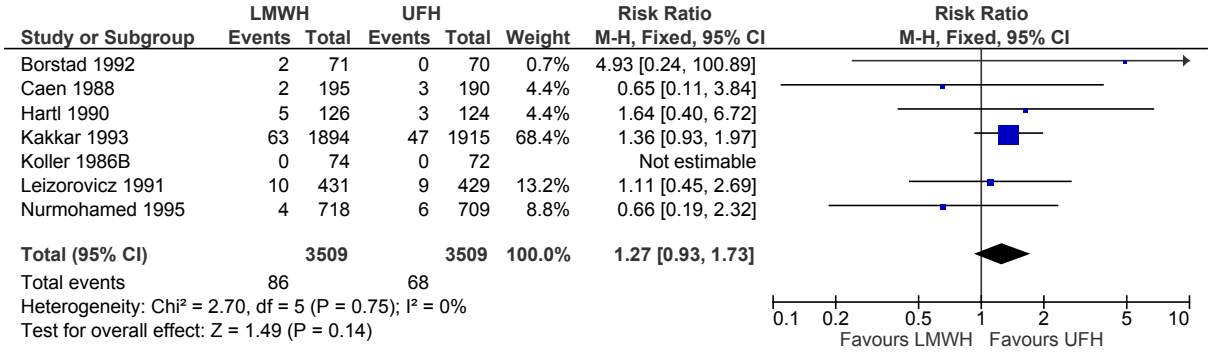


Figure 732: DVT (symptomatic and asymptomatic) (6-30 days)

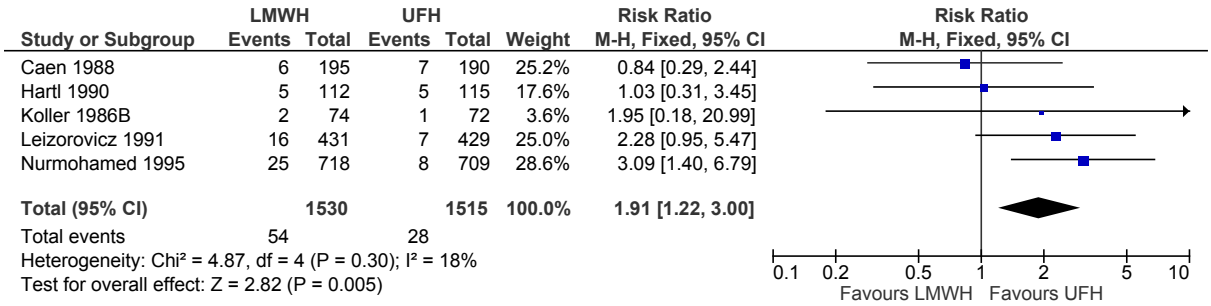


Figure 733: PE (6-30 days)

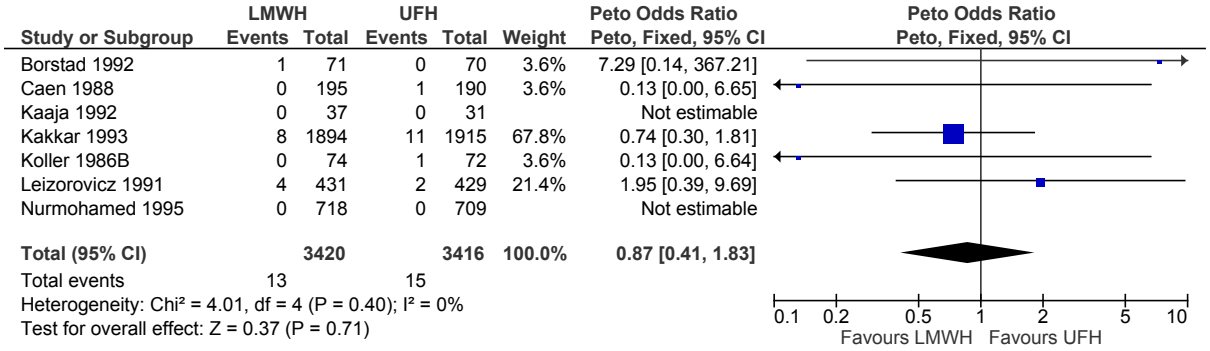


Figure 734: Major bleeding (5-30 days)

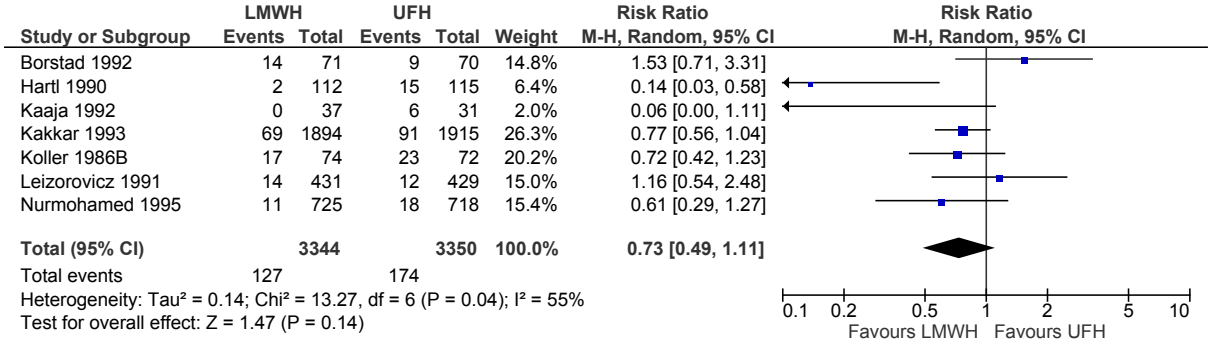
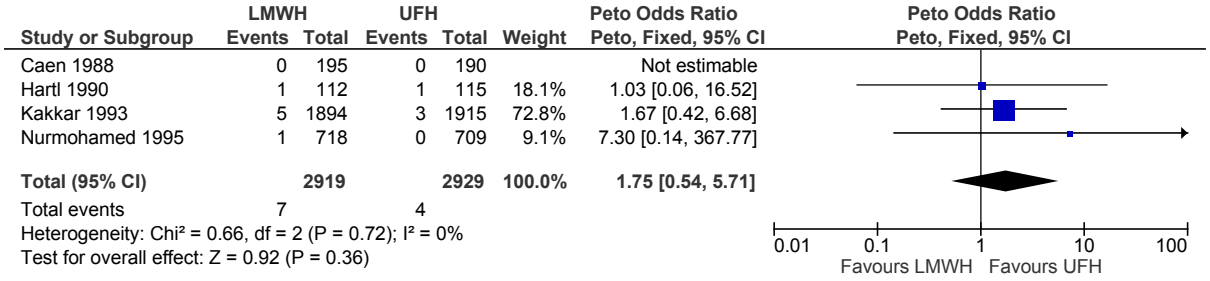


Figure 735: Fatal PE (6-30 days)



L.32.26 LMWH (standard dose; standard duration) versus no prophylaxis/mechanical

Figure 736: All-cause mortality (30 days)

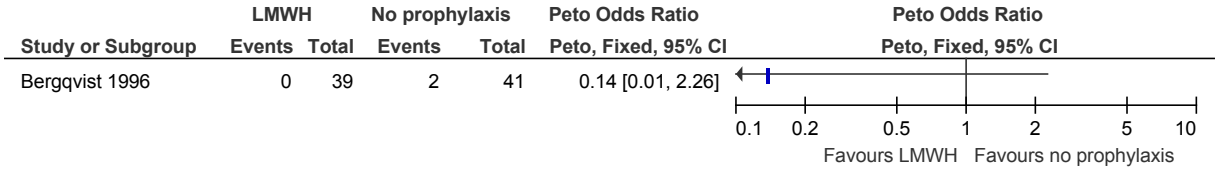


Figure 737: DVT (symptomatic and asymptomatic) (7-30 days)

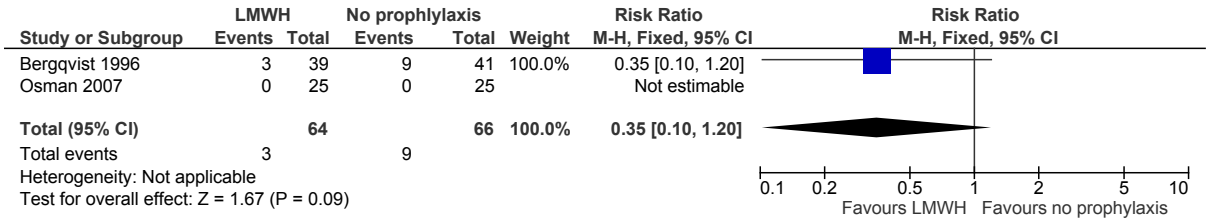


Figure 738: PE (14-30 days)

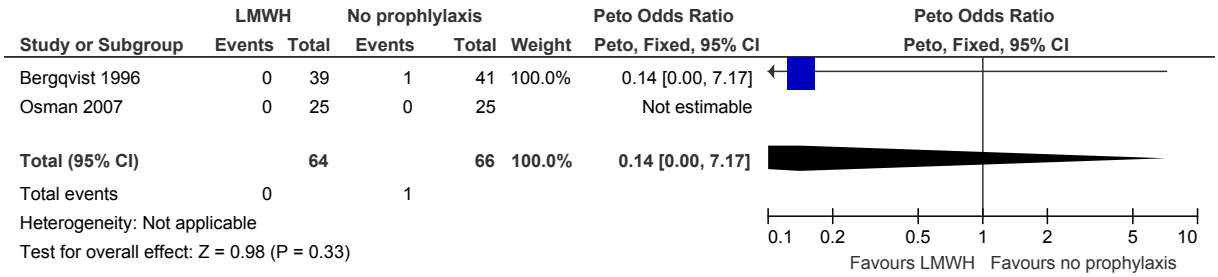
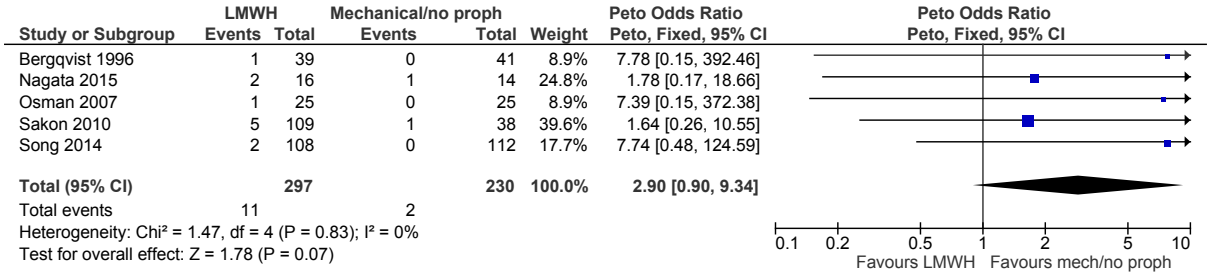


Figure 739: Major bleeding (11-30 days)



L.32.27 LMWH (standard dose; standard duration) versus IPCD (undefined)

Figure 740: DVT (symptomatic and asymptomatic) (30 days)

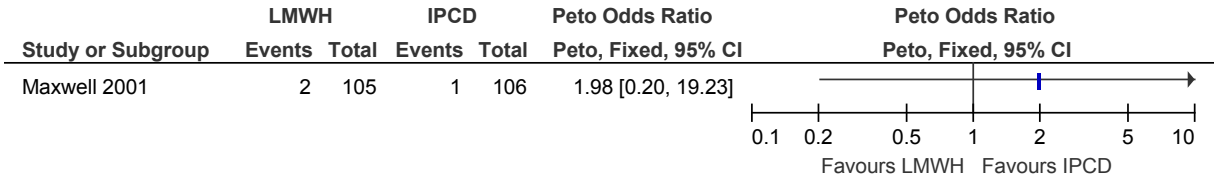


Figure 741: PE (30 days)

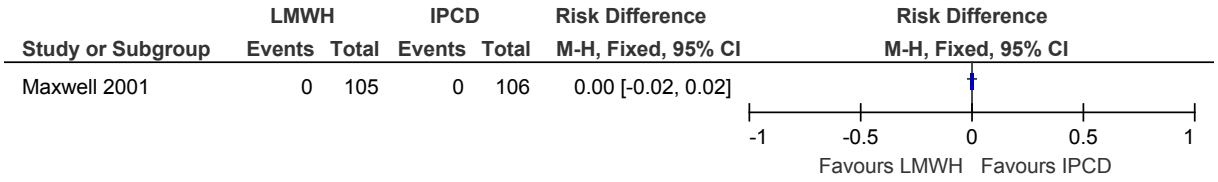
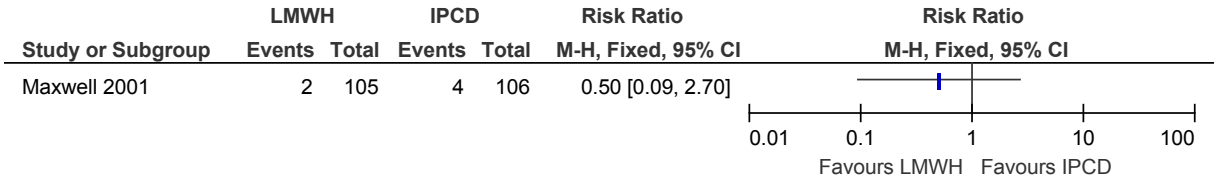


Figure 742: Thrombocytopenia (time-point not reported)



L.32.28 LMWH (standard dose; standard duration) versus UFH

Figure 743: All-cause mortality (8-30 days)

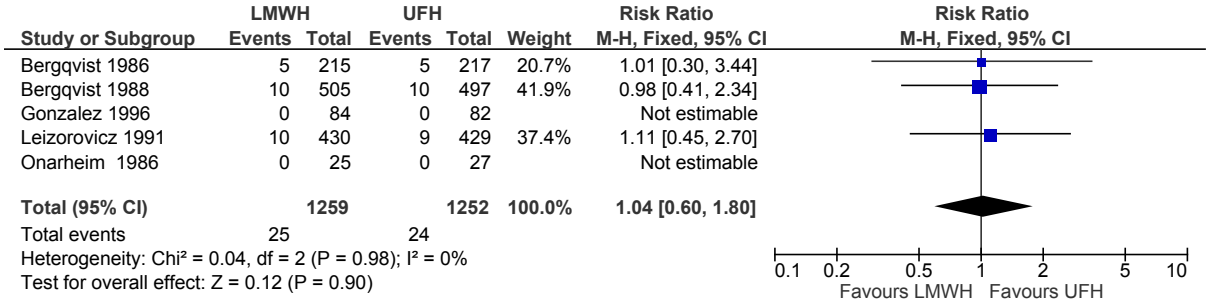


Figure 744: DVT (symptomatic and asymptomatic) (7-56 days)

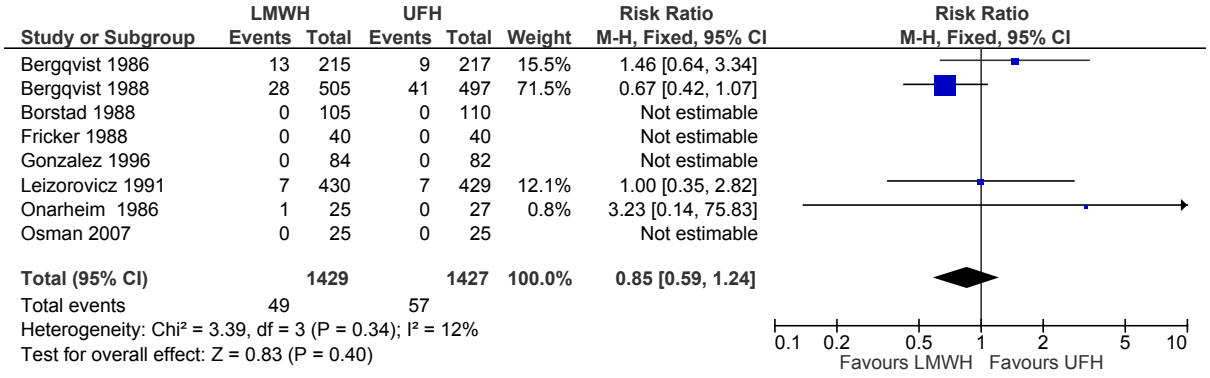


Figure 745: PE (7-56 days)

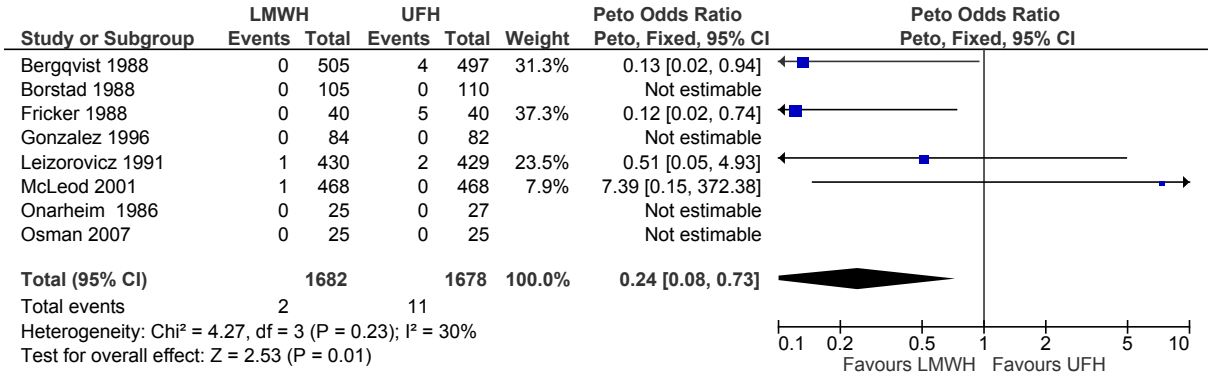


Figure 746: Major bleeding (8-30 days)

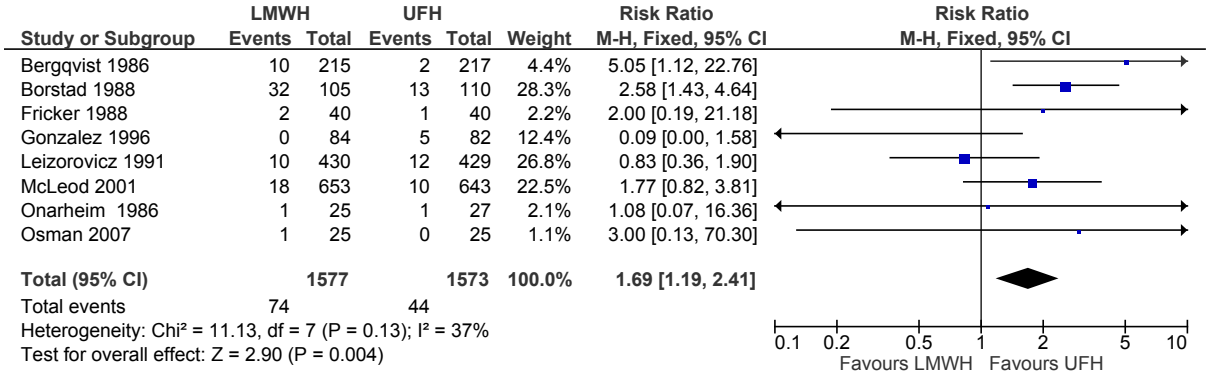
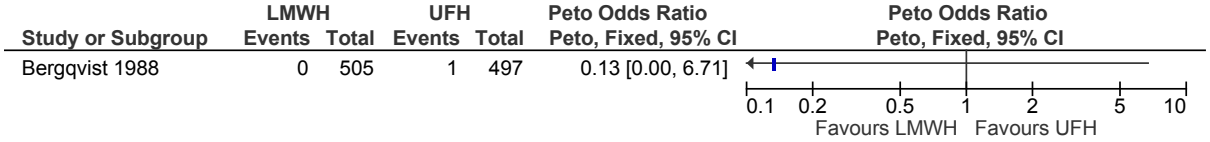


Figure 747: Fatal PE (30 days)



L.32.29 LMWH (high dose; standard duration) versus no prophylaxis

Figure 748: All-cause mortality (7 days)

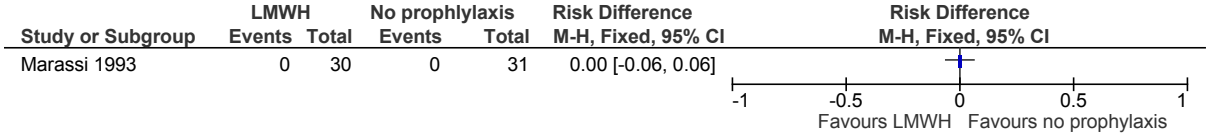
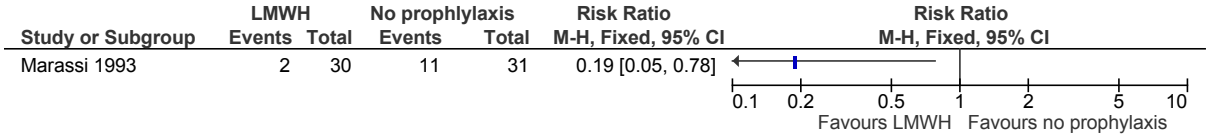


Figure 749: DVT (symptomatic and asymptomatic) (7 days)



L.32.30 LMWH (high dose; standard duration) versus UFH

Figure 750: All-cause mortality (time-point not reported)

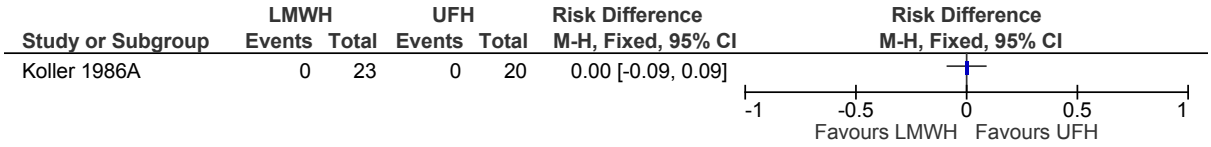


Figure 751: DVT (symptomatic and asymptomatic) (time-point not reported)

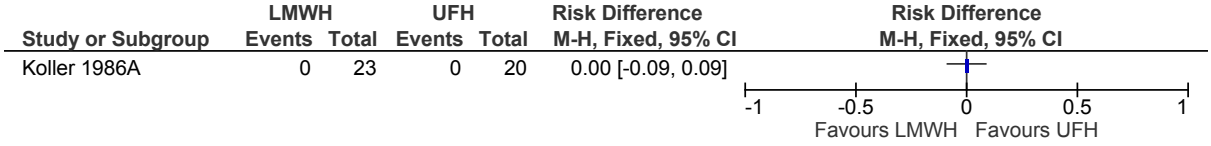
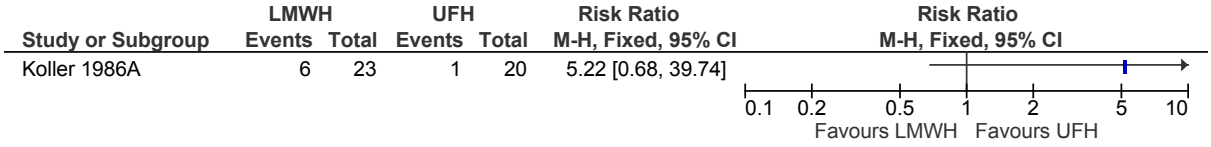


Figure 752: Major bleeding (time-point not reported)



L.32.31 LMWH (low dose; standard duration) versus LMWH (standard dose; standard duration)

Figure 753: All-cause mortality (8-30 days)

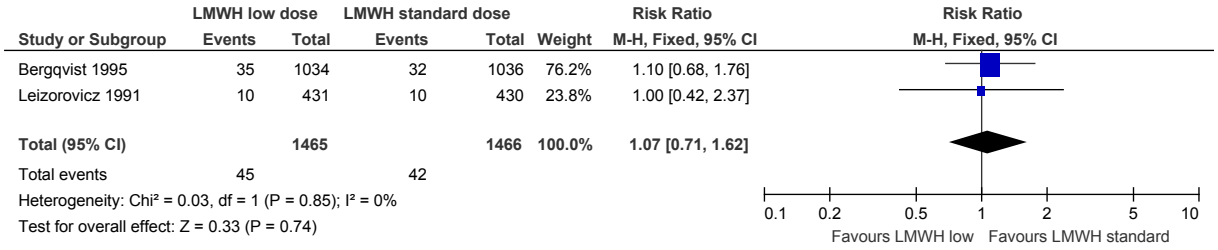


Figure 754: DVT (symptomatic and asymptomatic) (7-30 days)

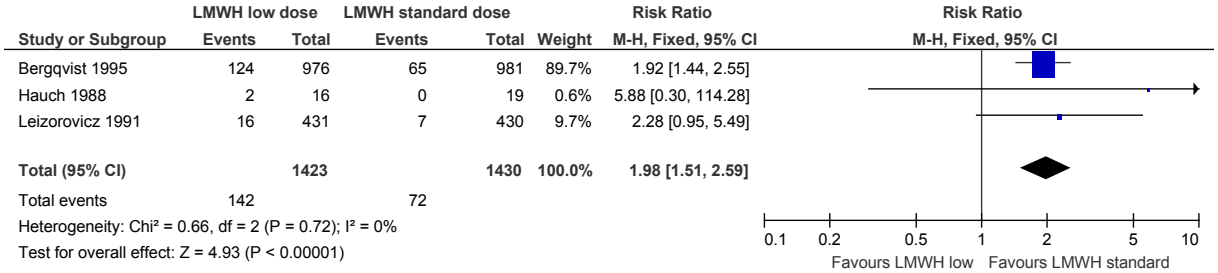


Figure 755: PE (30 days)

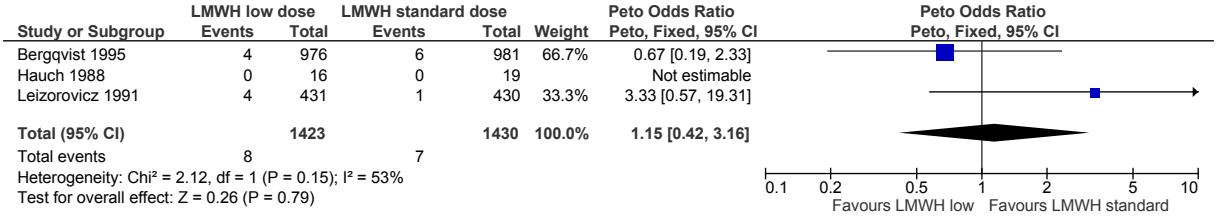


Figure 756: Major bleeding (30 days)

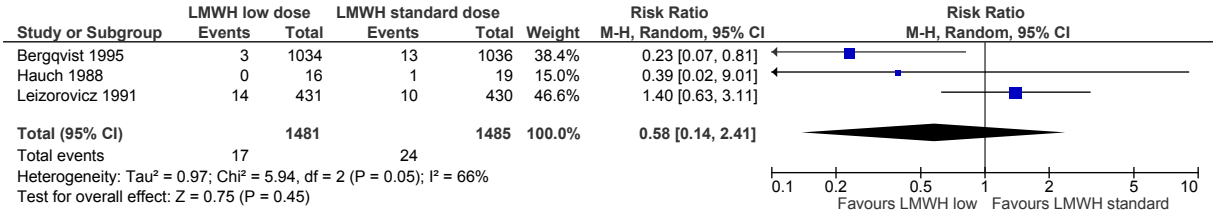
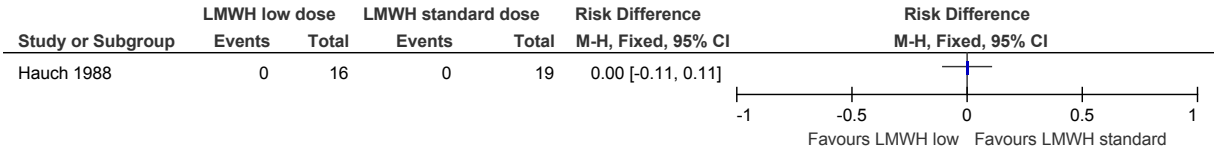


Figure 757: Fatal PE (30 days)



L.32.32 LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration)

Figure 758: All-cause mortality (60 days)

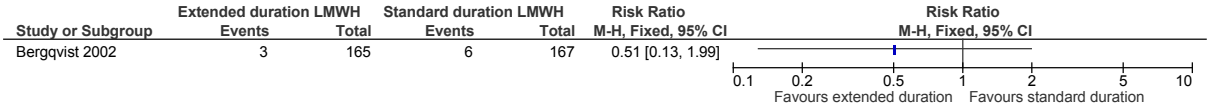


Figure 759: DVT (symptomatic and asymptomatic) (25-31 days)

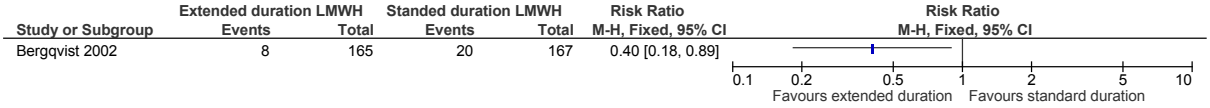


Figure 760: PE (90 days)

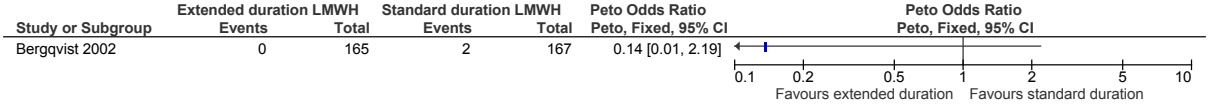


Figure 761: Major bleeding (90 days)

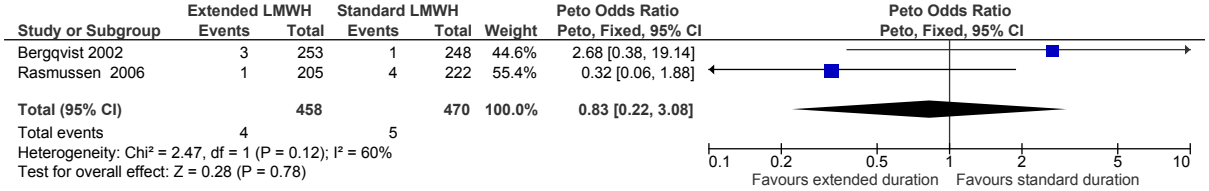
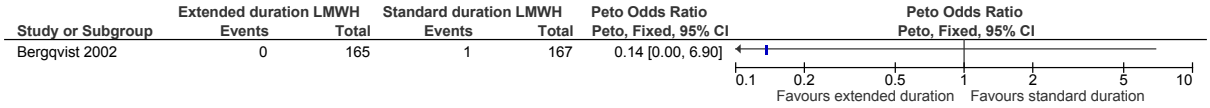


Figure 762: Fatal PE (90 days)



L.32.33 LMWH (high dose; extended duration) versus LMWH (high dose; standard duration)

Figure 763: All-cause mortality (90 days)

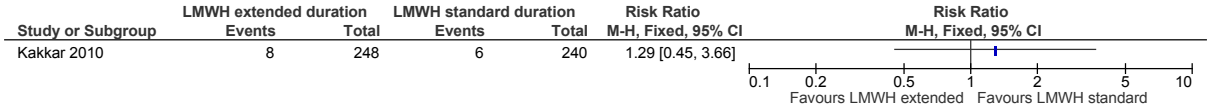


Figure 764: DVT (symptomatic and asymptomatic) (28 days)

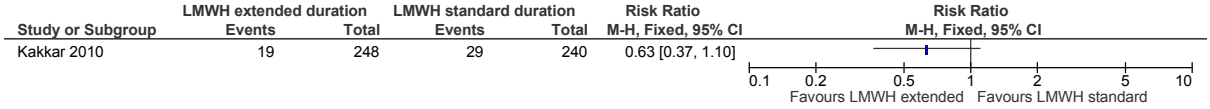


Figure 765: PE (28 days)

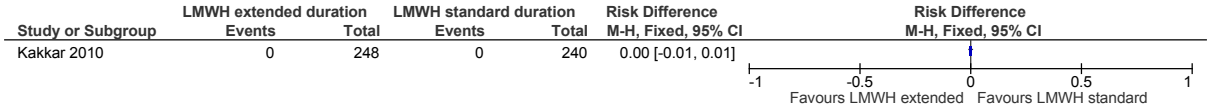
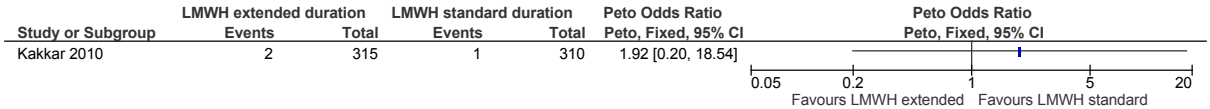


Figure 766: Major bleeding (22 days)



L.32.34 LMWH (standard dose; extended duration) + AES (undefined) versus LMWH (standard dose; standard duration) + AES (undefined)

Figure 767: All-cause mortality (60 days)

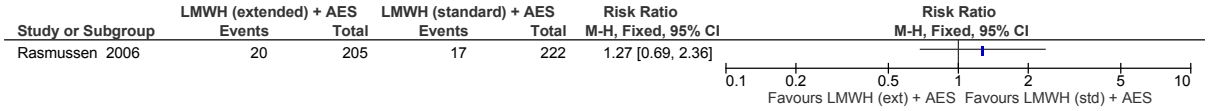


Figure 768: DVT (symptomatic and asymptomatic) (60 days)

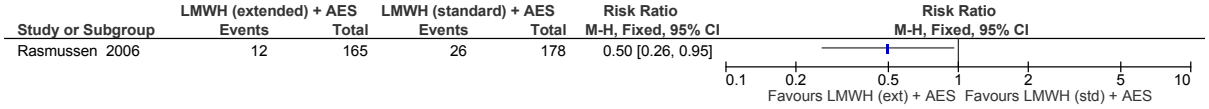


Figure 769: PE (28 days)

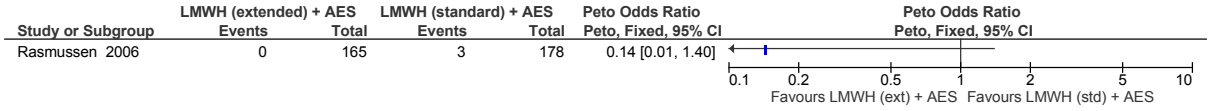
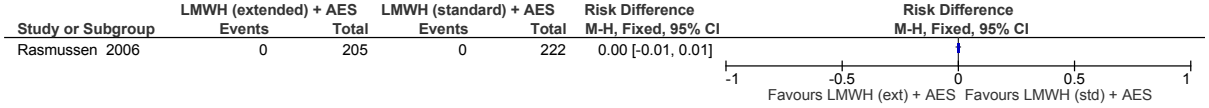


Figure 770: Fatal PE (28 days)



L.32.35 Fondaparinux versus LMWH (standard dose; standard duration)

Figure 771: All-cause mortality (32 days)

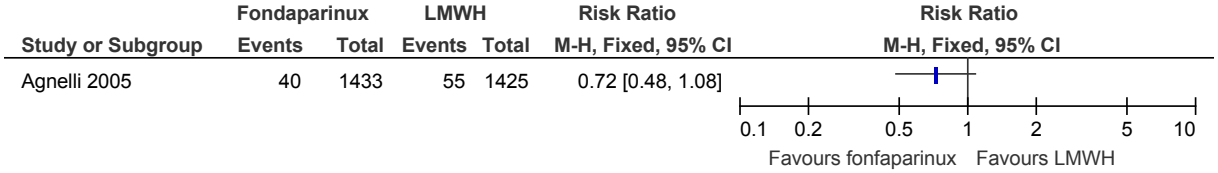


Figure 772: DVT (symptomatic and asymptomatic) (32 days)

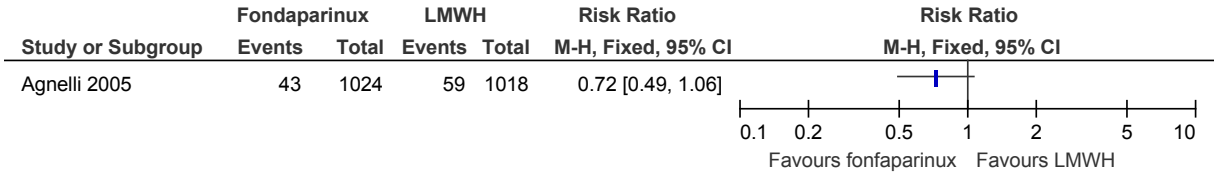


Figure 773: PE (32 days)

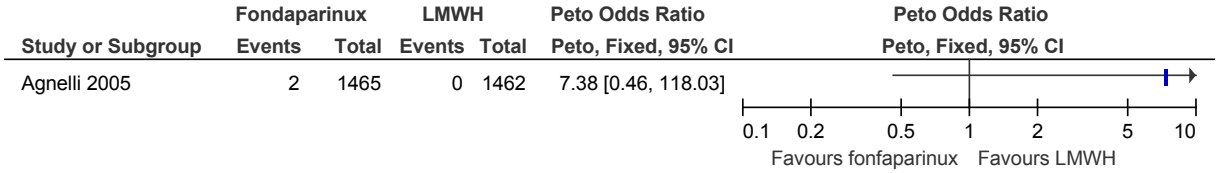


Figure 774: Major bleeding (5-11 days)

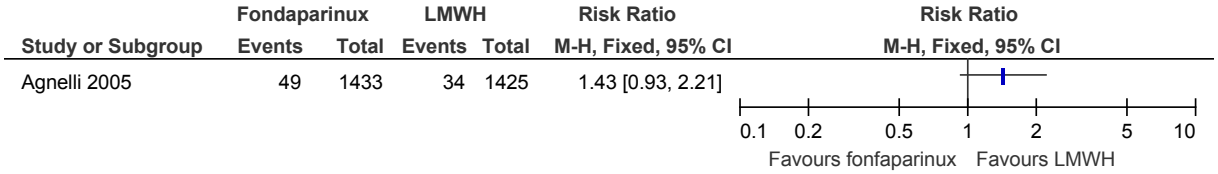
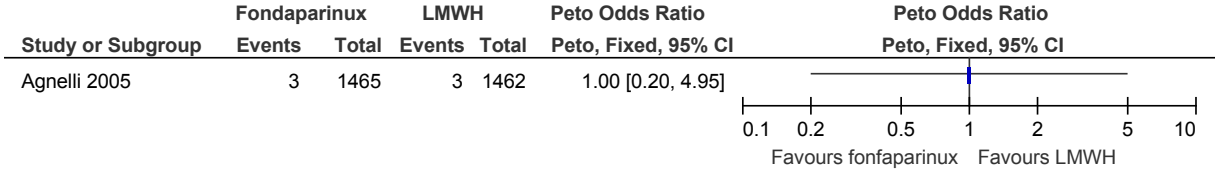


Figure 775: Fatal PE (32 days)



L.32.36 Fondaparinux + IPCD (undefined) versus IPCD (undefined)

Figure 776: All-cause mortality (32 days)

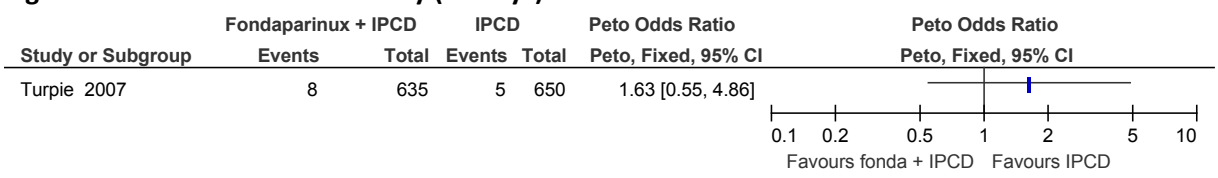


Figure 777: DVT (symptomatic and asymptomatic) (10 days)

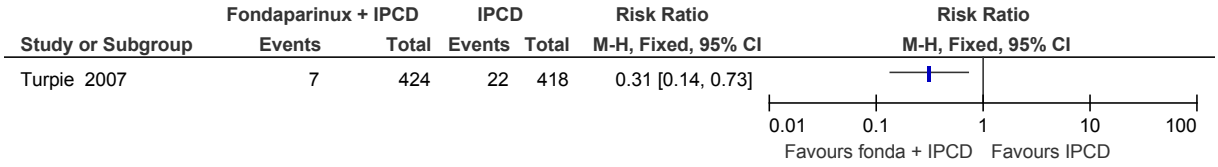


Figure 778: PE (32 days)

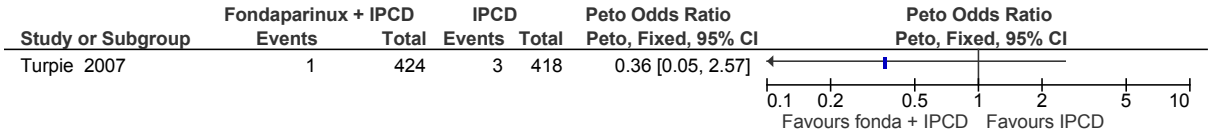
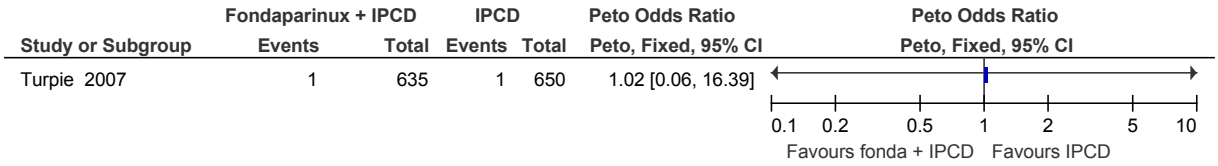
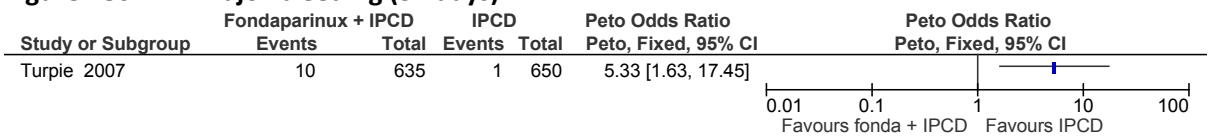


Figure 779: Fatal PE (32 days)



L.32.37 Fondaparinux versus no prophylaxis/mechanical

Figure 780: Major bleeding (32 days)



L.32.38 Fondaparinux + UFH + mechanical (AES + IPCD) versus LMWH (standard dose) + UFH + mechanical (AES + IPCD)

Figure 781: PE (time-point not reported)

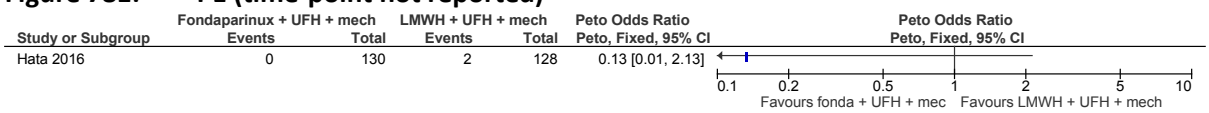
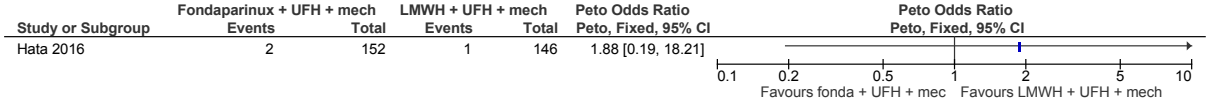
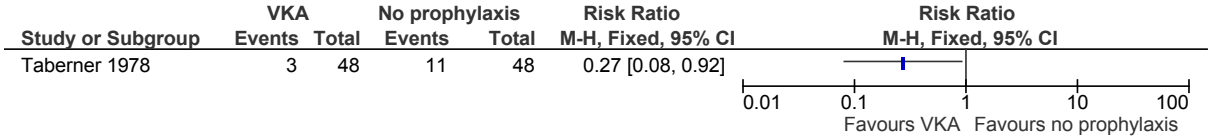


Figure 782: Major bleeding (time-point not reported)



L.32.39 VKA versus no prophylaxis

Figure 783: DVT (symptomatic and asymptomatic) (7 days)



L.33 Bariatric surgery

L.33.1 LMWH (standard dose pre-op, high post-op; standard duration) versus fondaparinux

Figure 784: DVT (symptomatic and asymptomatic) (14 days)

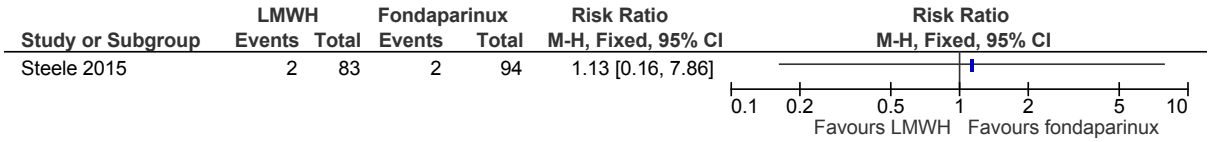
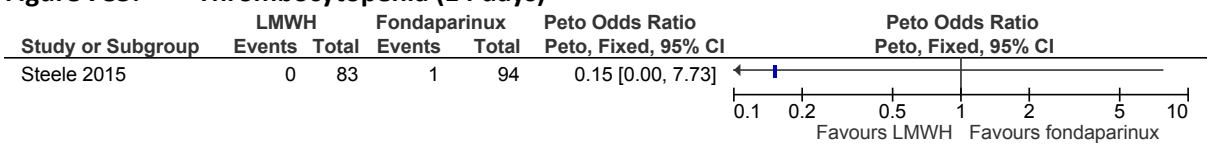


Figure 785: Thrombocytopenia (14 days)



L.33.2 LMWH (very high dose; standard duration) versus LMWH (high dose; standard duration)

Figure 786: DVT (symptomatic and asymptomatic) (90 days)

Study or Subgroup	LMWH (very high dose) Events	Total	LMWH (high dose) Events	Total	Risk Difference M-H, Fixed, 95% CI
Kalfarentzos 2001	0	30	0	30	0.00 [-0.06, 0.06]

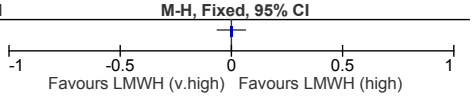
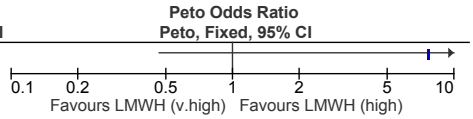


Figure 787: Major bleeding (time-point unclear)

Study or Subgroup	LMWH (very high dose) Events	Total	LMWH (high dose) Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Kalfarentzos 2001	2	30	0	30	7.65 [0.47, 125.22]



L.33.3 LMWH (very high dose; standard duration) + IPCD + AES versus LMWH (high dose; standard duration) + IPCD + AES

Figure 788: All-cause mortality (90 days)

Study or Subgroup	LMWH (v.high) +IPCD+AES Events	Total	LMWH (high) +IPCD+AES Events	Total	Risk Difference M-H, Fixed, 95% CI
Imberti 2014	0	119	0	131	0.00 [-0.02, 0.02]

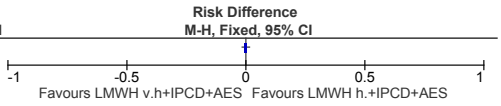


Figure 789: DVT (symptomatic and asymptomatic) (11 days)

Study or Subgroup	LMWH (v.high) +IPCD+AES Events	Total	LMWH (high) +IPCD+AES Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Imberti 2014	1	119	1	131	1.10 [0.07, 17.76]

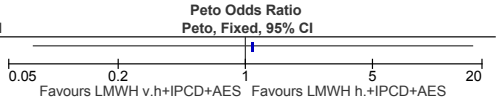


Figure 790: PE (11 days)

Study or Subgroup	LMWH (v.high) +IPCD+AES Events	Total	LMWH (high) +IPCD+AES Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Imberti 2014	0	119	1	131	0.15 [0.00, 7.51]

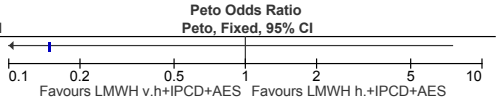
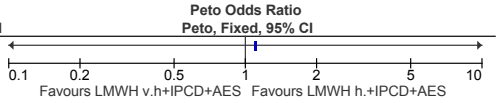


Figure 791: Heparin-induced thrombocytopenia (11 days)

Study or Subgroup	LMWH (v.high) +IPCD+AES Events	Total	LMWH (high) +IPCD+AES Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Imberti 2014	1	119	1	131	1.10 [0.07, 17.76]



L.34 Cardiac surgery

L.34.1 IPCD + AES + Aspirin versus AES + Aspirin

Figure 792: All-cause mortality (until discharge)

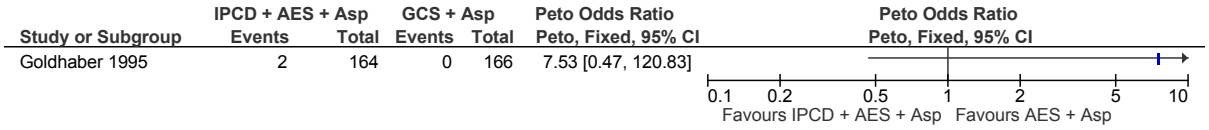


Figure 793: DVT (≥4 days post-op until discharge)

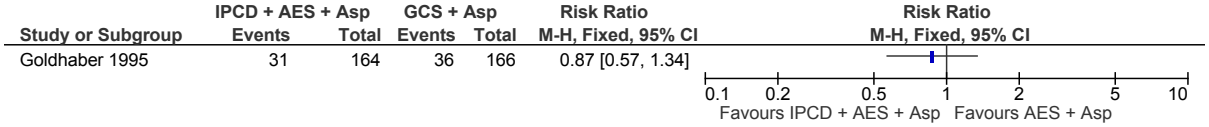


Figure 794: PE (until discharge)

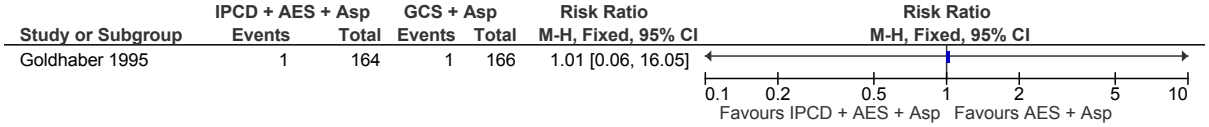
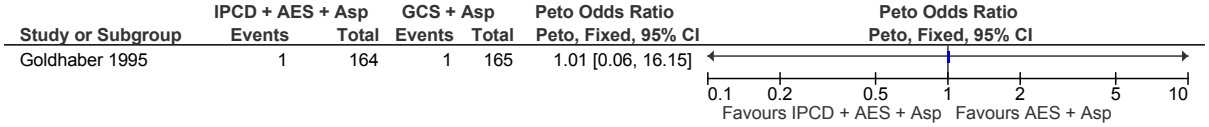


Figure 795: PE, fatal (until discharge)



L.34.2 Aspirin versus no prophylaxis

Figure 796: **All-cause mortality (30 days)**

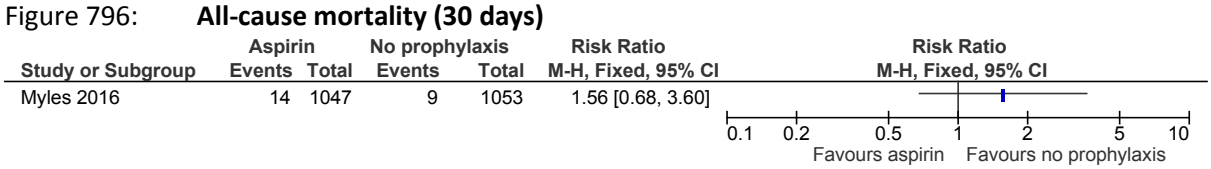


Figure 797: **PE (30 days)**

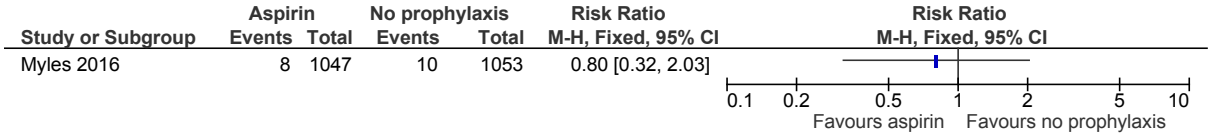
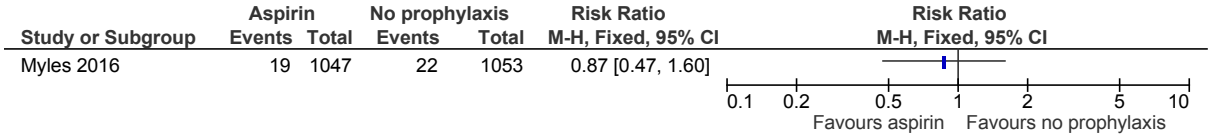
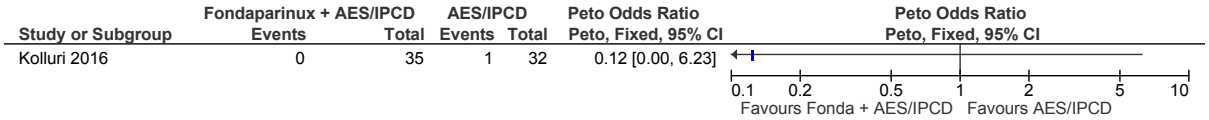


Figure 798: **Major bleeding (30 days)**



L.34.3 Fondaparinux + AES and/or IPCD versus AES and/or IPCD

Figure 799: DVT



L.35 Thoracic surgery

No relevant clinical studies were identified.

L.36 Vascular surgery

L.36.1 Overall strata (unspecified)

L.36.1.1 UFH versus no prophylaxis

Figure 800: DVT (timepoint not reported)

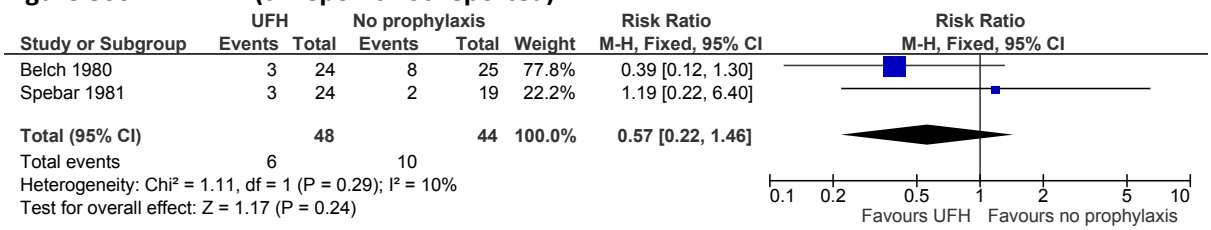


Figure 801: PE (timepoint not reported)

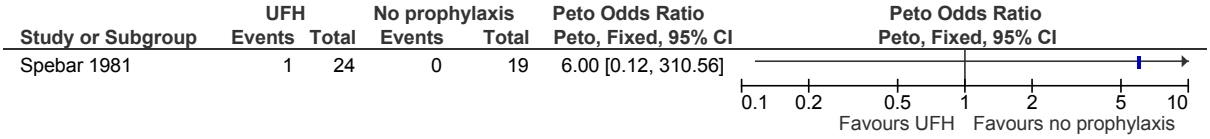
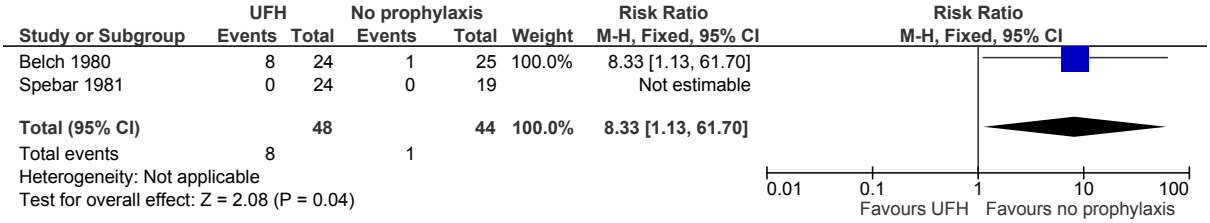


Figure 802: Major bleeding (timepoint not reported)



L.36.1.2 LMWH (standard dose pre-op/high dose post-op) versus UFH

Figure 803: All-cause mortality (timepoint not reported)

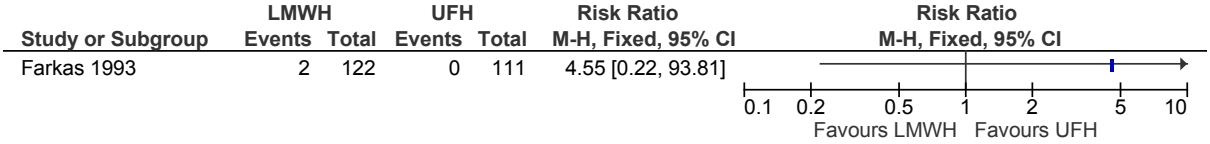


Figure 804: DVT (10 days)

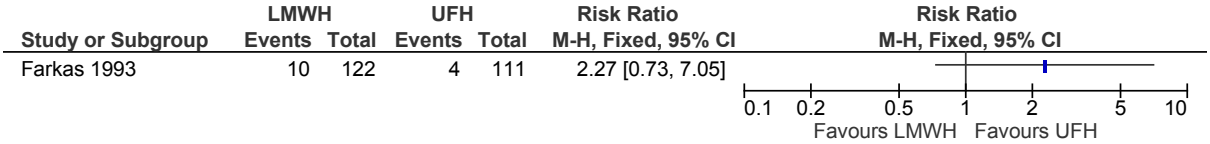


Figure 805: PE (timepoint not reported)

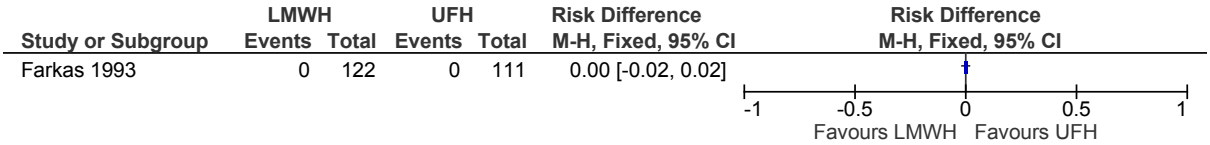
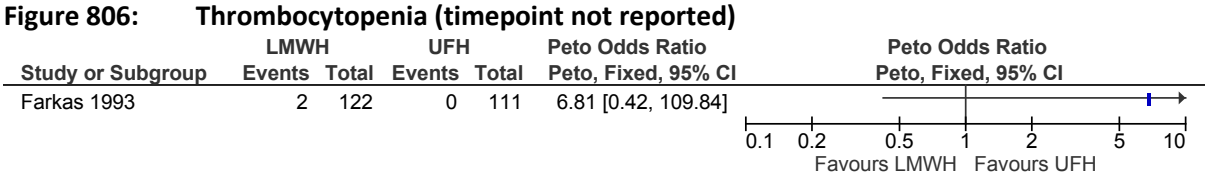


Figure 806: Thrombocytopenia (timepoint not reported)



L.36.2 Strata: Varicose vein surgery

L.36.2.1 LMWH (high dose) versus no prophylaxis

Figure 807: DVT (30 days)

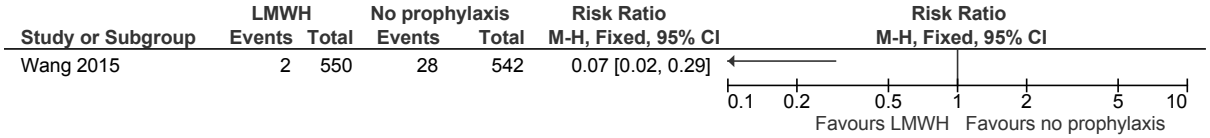


Figure 808: PE (30 days)

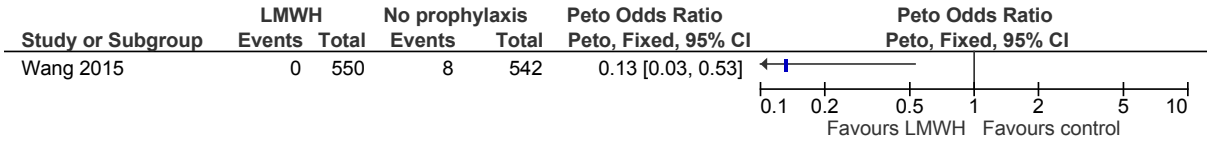
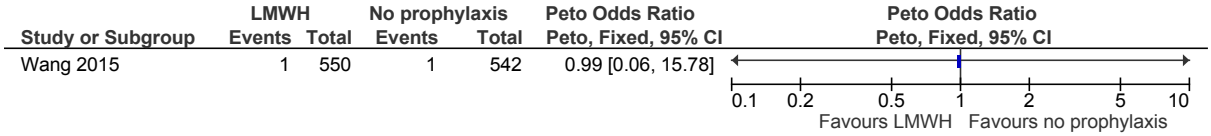


Figure 809: Major bleeding (30 days)



L.36.2.2 UFH versus no prophylaxis

Figure 810: DVT (30 days)

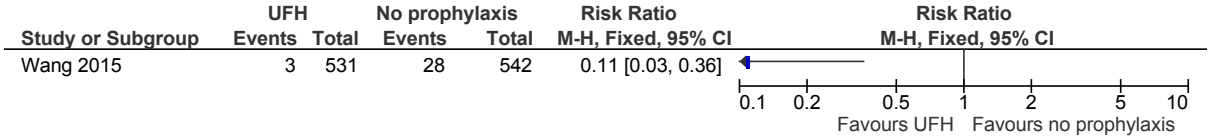


Figure 811: PE (30 days)

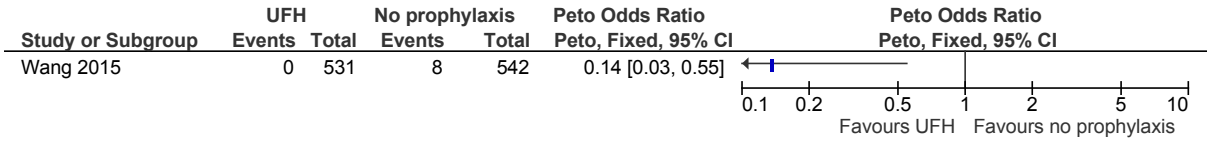
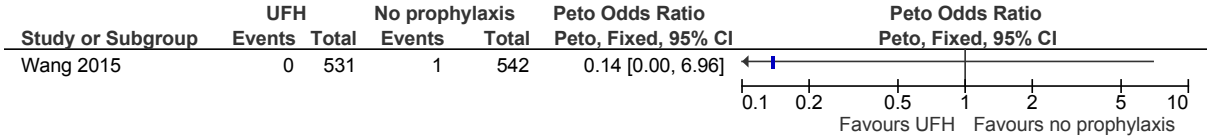


Figure 812: Major bleeding (30 days)



L.36.2.3 LMWH (high dose) versus UFH

Figure 813: DVT (30 days)

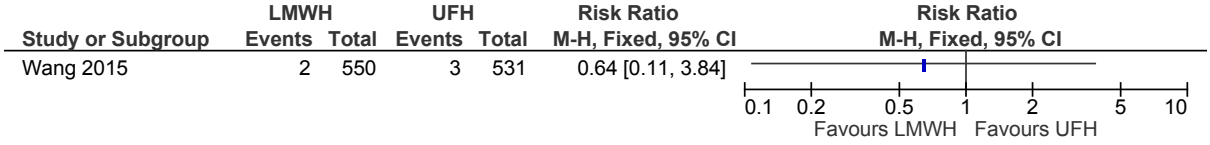


Figure 814: PE (30 days)

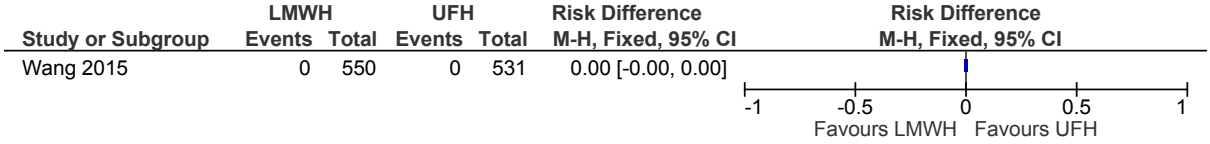
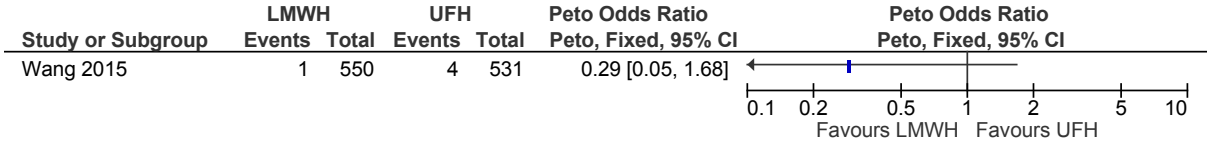


Figure 815: Major bleeding (30 days)



L.36.2.4 LMWH (standard dose) + AES + IPCD versus IPCD/AES

Figure 816: DVT (90 days)

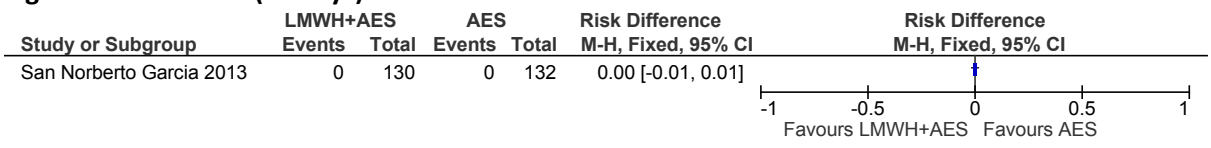


Figure 817: PE (90 days)

Study or Subgroup	LMWH+AES Events	LMWH+AES Total	AES Events	AES Total	Risk Difference M-H, Fixed, 95% CI
San Norberto Garcia 2013	0	130	0	132	0.00 [-0.01, 0.01]

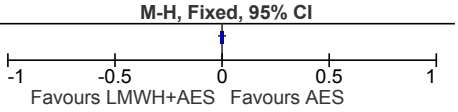
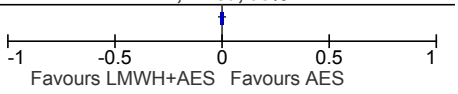


Figure 818: Major bleeding (90 days)

Study or Subgroup	LMWH+AES Events	LMWH+AES Total	AES Events	AES Total	Risk Difference M-H, Fixed, 95% CI
San Norberto Garcia 2013	0	130	0	132	0.00 [-0.01, 0.01]



L.36.2.5 AES versus no prophylaxis

Figure 819: All-cause mortality (14 days)

Study or Subgroup	AES Events	AES Total	No prophylaxis Events	No prophylaxis Total	Risk Difference M-H, Fixed, 95% CI
Ye 2016	0	200	0	200	0.00 [-0.01, 0.01]

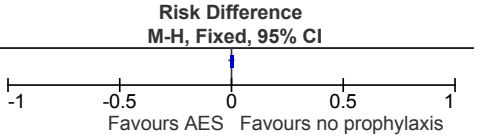


Figure 820: DVT (14 days)

Study or Subgroup	AES Events	AES Total	No prophylaxis Events	No prophylaxis Total	Risk Difference M-H, Fixed, 95% CI
Ye 2016	0	200	0	200	0.00 [-0.01, 0.01]

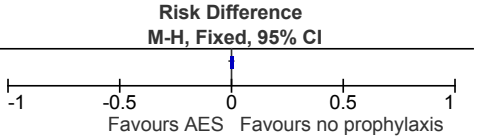


Figure 821: PE (14 days)

Study or Subgroup	AES Events	AES Total	No prophylaxis Events	No prophylaxis Total	Risk Difference M-H, Fixed, 95% CI
Ye 2016	0	200	0	200	0.00 [-0.01, 0.01]

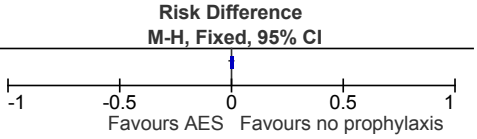


Figure 822: HRQOL (Aberdeen Varicose Vein Symptoms Severity Score)

Study or Subgroup	AES Mean	AES SD	AES Total	No prophylaxis Mean	No prophylaxis SD	No prophylaxis Total	Mean Difference IV, Fixed, 95% CI
Ye 2016	8.5	3.6	200	8	3.4	200	0.50 [-0.19, 1.19]

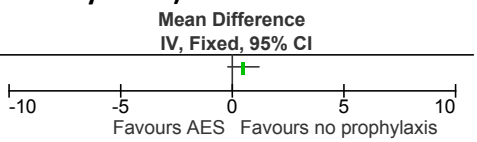


Figure 823: HRQOL (Venous clinical severity score)

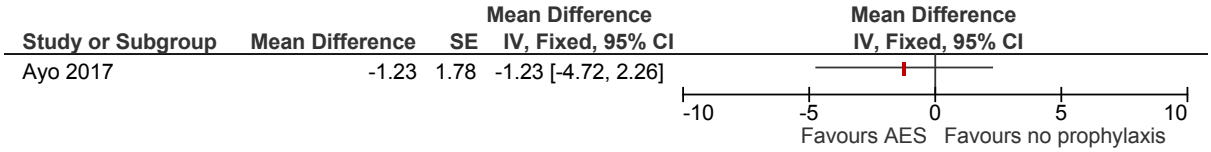
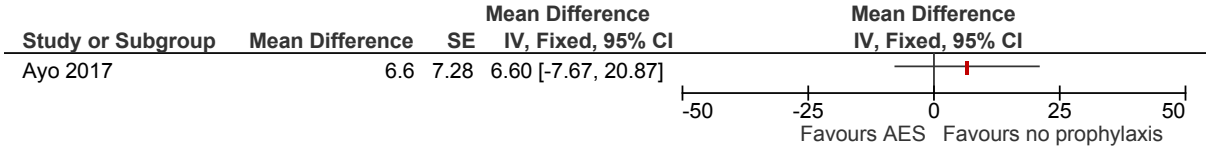


Figure 824: HRQOL (Chronic venous insufficiency questionnaire)



L.36.3 Strata: Lower limb amputation

L.36.3.1 LMWH (standard dose) versus UFH

Figure 825: DVT (5-8 days post-op)

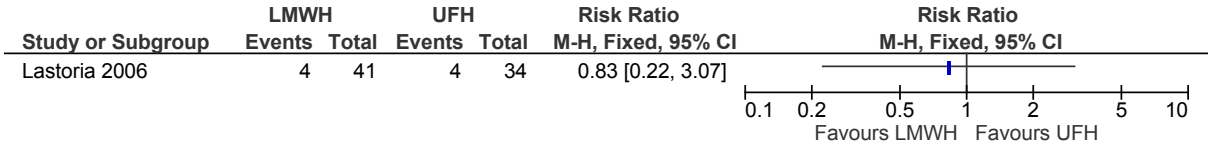
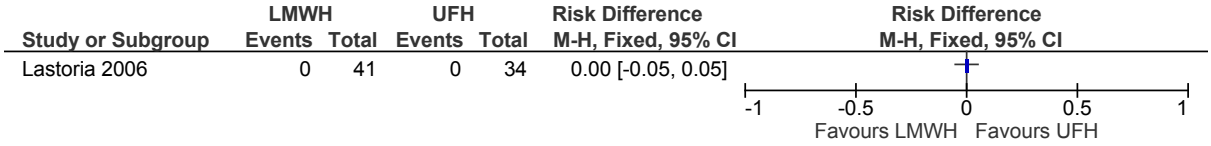


Figure 826: Major bleeding (timepoint not reported)



L.37 Head and neck surgery

L.37.1 Oral and maxillofacial surgery

No relevant clinical studies were identified.

L.37.2 Ear, nose and throat (ENT) surgery

No relevant clinical studies were identified.

Appendix M: Network meta-analyses (NMAs)

M.1 Network meta-analysis for elective hip replacement surgery

M.1.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in Appendix K and forest plots in Appendix L) does not help inform which intervention is most effective as VTE prophylaxis in patients undergoing elective hip replacement surgery. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different treatments; in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial.
- There are frequently multiple overlapping comparisons that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions. In this case the outcomes were defined as:

- Deep vein thrombosis (DVT; symptomatic and asymptomatic)
- Pulmonary embolism (PE)
- Major bleeding

The analysis also provided 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.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term “network” better describes the data structure, whereas “mixed treatments” could easily be misinterpreted as referring to combinations of treatments.

M.1.2 Methods

M.1.2.1 Study selection

To estimate the relative risks, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

M.1.2.2 Outcome measures

The NMA evidence reviews for interventions considered three clinical efficacy outcomes identified from the clinical evidence review; number of people with DVT, number of people with PE and number of people with major bleeding. Other outcomes were not considered for the NMA as they were infrequently reported across the studies. The guideline committee considered that these outcomes were the most critical clinical outcomes for testing effectiveness of VTE prophylaxis.

M.1.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical evidence review already presented in Chapter 26 of the full guideline and in Appendix H. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in each network are shown in **Table 237**.

Table 237: Treatments included in network meta-analysis

Network 1: Number of people with DVT	Network 2: Number of people with PE	Network 3: Number of people with major bleeding
No prophylaxis	No prophylaxis	No prophylaxis/mechanical
LMWH (standard dose; standard duration)	LMWH (standard dose; standard duration)	UFH (standard duration)
UFH (standard duration)	LMWH (standard dose) + AES	LMWH (high dose; standard duration)
LMWH (standard dose) + AES	IPCD (length unspecified)	LMWH (standard dose; standard duration)
LMWH (high dose; standard duration)	UFH (standard duration)	Fondaparinux
IPCD	Rivaroxaban	LMWH (low dose; post-op)
LMWH (standard dose; extended duration)	LMWH (standard dose; extended duration)	VKA (standard duration)
Dabigatran	LMWH (high dose; standard duration)	Dabigatran
Foot pump	Dabigatran	Apixaban
Apixaban	Foot pump	Rivaroxaban
Rivaroxaban	Apixaban	LMWH (standard dose; extended duration)

Network 1: Number of people with DVT	Network 2: Number of people with PE	Network 3: Number of people with major bleeding
VKA (standard duration)	AES (length unspecified)	LMWH (low dose; pre-op)
UFH (extended duration)	LMWH (low dose) + AES	VKA (extended duration)
Aspirin	Fondaparinux + AES	LMWH (standard dose; standard duration) followed by aspirin (extended duration)
LMWH (low dose) + AES	LMWH (standard dose; extended duration) + AES	LMWH (high dose; extended duration)
LMWH (extended duration) + AES	Aspirin (standard duration)	-
Fondaparinux + AES	LMWH (standard dose; standard duration) followed by aspirin (extended duration)	-
AES (length unspecified)	VKA (standard duration)	-
LMWH (low dose; pre-op)	UFH + AES	-
LMWH (low dose; post-op)	AES (above-knee)	-
VKA (extended duration)	LMWH (high dose) + AES	-
AES (above-knee)	VKA (extended duration)	-
LMWH (high dose) + AES	LMWH (high dose; extended duration)	
UFH + AES	-	-
Foot pump + AES	-	-
LMWH (high dose; extended duration)	-	

M.1.2.4 Baseline risks

The baseline risk is defined as the risk of achieving the outcome of interest in the baseline treatment arm of the included trials. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks. However, the majority of the trials were old studies that reported very high risk of DVT and PE in the no prophylaxis arm that the orthopaedic subgroup considered to be not reflective of the baseline risk in the UK. Hence, for the purpose of calculating the relative risks of these events for presentation in this appendix, the baseline risk values were obtained from a large observational study that used data from the UK National Joint Registry (NJR).[451] For full details please refer to HE write-up (Appendix P, section P.1.3.3).

M.1.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome subgroup, a diagram of the evidence network is presented in section M.1.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. Due to the sparse nature of the networks

(few studies per direct treatment comparison), the between-study heterogeneity parameter is imprecisely estimated in a random effects model. Therefore it is beneficial to apply informative priors in order to restrict the prior distribution for heterogeneity to avoid unreasonably wide credible intervals. Turner et al (2015)[946] derived a novel set of predictive distributions for the degree of heterogeneity across 80 different settings. Appropriate predictive distributions for heterogeneity were chosen from Turner et al (2015)[946] and used directly as informative priors. The log normal (μ, σ^2) predictive distributions obtained for the between-study heterogeneity in a future meta-analysis presented in Table IV[946] were selected according to the outcome and treatment comparison. For the DVT and PE NMAs the distributions defined by the outcome of "general physical health indicators" and by the intervention/comparison type "non-pharmacological vs. pharmacological" were chosen (LN[-1.26, 1.25^2]). For the major bleeding NMA the distributions defined by the outcome of "adverse events" and by the intervention/comparison type "non-pharmacological vs. pharmacological" were chosen (LN[-0.84, 1.24^2]). These distributions were chosen as they represented outcomes measured by an assessor, whose method of measurement as well as judgement may influence the outcome (as studies provided slightly variable ways of defining these critical outcomes), and the interaction aspect encompassed both the pharmacological and mechanical prophylaxis options covered in our review protocol.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 26, and Appendix H).

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and treatment specific absolute probability respectively. Then:

$$\tilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$\boldsymbol{p} = \frac{\boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}{\mathbf{1} + \boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability ($\boldsymbol{p_b}$) to get treatment specific relative risks ($\boldsymbol{rr_b}$):

$$\boldsymbol{p_b} = \frac{\boldsymbol{e}^{\boldsymbol{BO}}}{\mathbf{1} + \boldsymbol{e}^{\boldsymbol{BO}}}$$

$$\boldsymbol{rr_b} = \frac{\boldsymbol{p}}{\boldsymbol{p_b}}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

We also calculated the overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the relative risks from the direct evidence (from pair-wise meta-analysis) to the relative risks from the combined direct and indirect evidence (from NMA). We further tested for inconsistency by developing inconsistency models for networks of binary outcomes using the TSD 4 template from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). We compared the posterior mean of the residual deviance between the consistency and inconsistency models to see which was a better fit to the data (closest to the number of trial arms in each network) and checked the difference in deviance information criterion (DIC) values between the two models was small (less than 3-5) or if it was larger, that the smaller DIC and hence better fitting model was the consistency model. No inconsistency was identified.

M.1.3 Results

M.1.3.1 Deep vein thrombosis (symptomatic and asymptomatic)

Included studies

44 studies were identified as reporting on DVT outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 42 studies involving 26 treatments were included in the network for DVT (symptomatic and asymptomatic). The network can be seen in Figure 827 and the trial data for each of the studies included in the NMA are presented in **Table 238**.

Figure 827: Network diagram for DVT (symptomatic and asymptomatic)

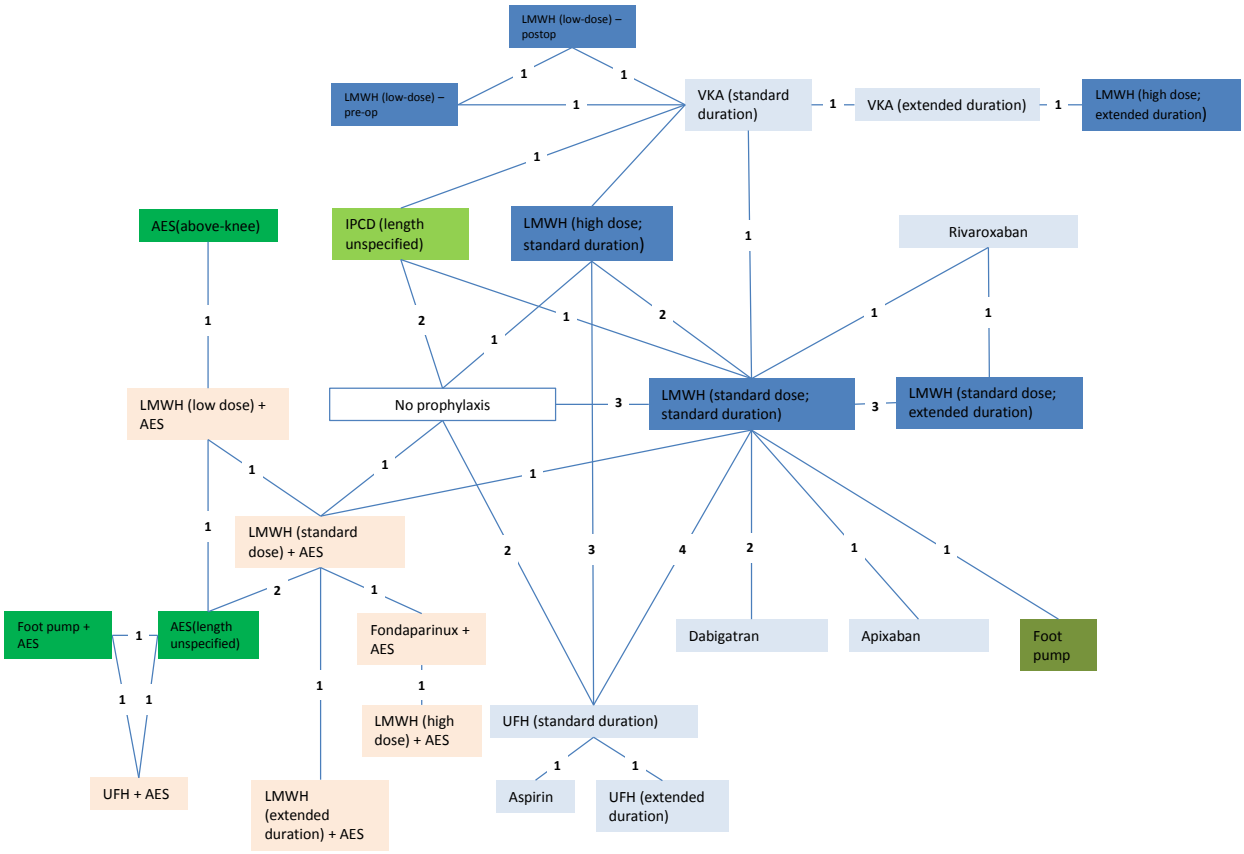


Table 238: Study data for DVT network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
				N	NA	N	NA	N	NA
Kalodiki 1996 [472]	No prophylaxis	LMWH (standard dose; standard duration)	LMWH (standard dose) + AES	13	14	12	32	8	32
Bergqvist 1996B [92]	No prophylaxis	LMWH (standard dose; standard duration)	-	43	116	21	117	NA	NA
Tørholm 1991 [941]	No prophylaxis	LMWH (standard dose; standard duration)	-	19	54	9	58	NA	NA
Hampson 1974 [382]	No prophylaxis	UFH (standard duration)	-	28	52	22	48	NA	NA
Mannucci 1976 [604]	No prophylaxis	UFH (standard duration)	-	36	75	14	68	NA	NA
Turpie 1986 [952]	No prophylaxis	LMWH (high dose; standard	-	20	39	4	37	NA	NA

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
		duration)							
Hull 1990	No prophylaxis	IPCD (length unspecified)	-	36	152	77	158	NA	NA
Gallus 1983 [334]	No prophylaxis	IPCD (length unspecified)	-	25	47	15	43	NA	NA
Colwell 1994 [204]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	28	136	21	142	8	136
Avikainen 1995 [57]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	1	79	4	79	NA	NA
Eriksson 1991A [289]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	19	63	25	59	NA	NA
Planes 1990A (Trial3) [758]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	15	120	27	106	NA	NA
Planes 1990A (Trial1) [758]	LMWH (standard dose; standard duration)	LMWH (high dose; standard duration)	-	12	150	5	78	NA	NA
Hardwick 2011 [389]	LMWH (standard dose; standard duration)	IPCD (length unspecified)	-	8	190	8	196	NA	NA
Comp 2001 [209]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	39	138	15	152	NA	NA
Lassen 1998 [528]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	12	102	5	113	NA	NA
Planes 1996 [757]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	17	88	6	85	NA	NA
Eriksson 2011 [292]	LMWH (standard dose; standard duration)	Dabigatran	-	67	783	60	791	NA	NA
Eriksson 2007 [288]	LMWH (standard dose; standard duration)	Dabigatran	-	57	897	45	880	NA	NA
Warwick 1998 [994]	LMWH (standard dose; standard	Foot pump	-	18	138	24	136	NA	NA

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
	duration)								
Lassen 2010 [535]	LMWH (standard dose; standard duration)	Apixaban	-	68	1911	22	1944	NA	NA
Kakkar 2008 [467]	LMWH (standard dose; standard duration)	Rivaroxaban	-	71	869	14	864	NA	NA
Francis 1997A [315]	LMWH (standard dose; standard duration)	VKA (standard duration)	-	49	190	28	192	NA	NA
Kakkar 2000 [468]	UFH (standard duration)	LMWH (high dose; standard duration)	-	24	116	9	101	NA	NA
Levine 1991 [551]	UFH (standard duration)	LMWH (high dose; standard duration)	-	61	263	50	258	NA	NA
Manganelli 1998 [601]	UFH (standard duration)	UFH (extended duration)	-	4	33	6	28	NA	NA
Zanasi 1988 [1039]	UFH (standard duration)	Aspirin	-	10	25	7	19	NA	NA
Fuji 2008A [328]	LMWH (standard dose) + AES	LMWH (low dose) + AES	AES (length unspecified)	27	80	21	81	36	86
Dahl 1997 [226]	LMWH (standard dose) + AES	LMWH (extended duration) + AES	-	33	104	22	114	NA	NA
Lassen 2002 [526]	LMWH (standard dose) + AES	Fondaparinux + AES	-	83	918	36	908	NA	NA
Samama 1997 [844]	LMWH (standard dose) + AES	AES (length unspecified)	-	11	78	28	75	NA	NA
Warwick 1995A [996]	LMWH (standard dose) + AES	AES (length unspecified)	-	22	78	33	78	NA	NA
Paeiment 1987 [722]	IPCD (length unspecified)	VKA (standard duration)	-	11	66	12	72	NA	NA
Lassen 1991 [529]	AES (above-knee)	LMWH (low dose) + AES	-	53	1558	12	1595	NA	NA
Eriksson 2008 [291]	LMWH (standard dose; extended duration)	Rivaroxaban	-	81	338	36	337	44	336
Hull 2000 [440]	VKA (standard duration)	LMWH (low dose; pre-op)	LMWH (low dose; post-op)	8	176	3	184	NA	NA
Prandoni 2002 [771]	VKA (standard duration)	VKA (extended duration)	-	29	93	44	97	NA	NA

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
Turpie 2002K [954]	Fondaparinux + AES	LMWH (high dose) + AES	-	44	784	65	796	NA	NA
Moskovitz 1978[657]	AES (length unspecified)	UFH + AES	-	19	28	8	32	NA	NA
Fordyce 1992 [312]	AES (length unspecified)	Foot pump + AES		4	39	16	40	NA	NA
Samama 2002 [845]	LMWH (high dose; extended duration)	VKA (extended duration)	-	20	636	15	643	NA	NA
Santori 1994 [850]	UFH + AES	Foot pump + AES		23	65	9	67	NA	NA

N; number of events, NA; number analysed

NMA results

Table 239 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 239: Risk ratios for DVT (symptomatic and asymptomatic)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	LMWH (standard dose; standard duration)	0.46 (0.33, 0.63)	0.46 (0.23, 0.81)
	UFH (standard duration)	0.61 (0.45, 0.85)	0.60 (0.28, 1.03)
	LMWH (standard dose) + AES	0.27 (0.15, 0.50)	0.14 (0.07, 0.59)
	LMWH (high dose; standard duration)	0.21 (0.08, 0.56)	0.28 (0.10, 0.67)
	IPCD	0.53 (0.40, 0.69)	0.80 (0.34, 1.41)
	LMWH (standard dose; extended duration)	-	0.19 (0.05, 0.57)
	Dabigatran	-	0.40 (0.11, 1.05)
	Foot pump	-	0.62 (0.11, 1.83)
	Apixaban	-	0.16 (0.03, 0.76)
	Rivaroxaban	-	0.06 (0.01, 0.29)
	VKA (standard duration)	-	0.44 (0.11, 1.13)
	UFH (extended duration)	-	0.96 (0.15, 2.92)
	Aspirin	-	0.54 (0.07, 1.87)
	LMWH (low dose) + AES	-	0.13 (0.02, 0.89)
	LMWH (extended duration) + AES	-	0.08 (0.01, 0.61)
	Fondaparinux + AES	-	0.07 (0.01, 0.49)
	AES (length unspecified)	-	0.30 (0.08, 1.46)
	LMWH (low dose; pre-op)	-	0.19 (0.02, 1.00)
	LMWH (low dose; post-op)	-	0.23 (0.03, 1.12)
	VKA (extended duration)	-	0.16 (0.01, 1.08)
	AES (above-knee)	-	0.23 (0.02, 2.04)
	LMWH (high dose) + AES	-	0.10 (0.01, 1.07)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	UFH + AES		0.27 (0.04, 1.82)
	Foot pump + AES	-	0.32 (0.04, 2.11)
	LMWH (high dose; extended duration)		0.12 (0.00, 1.20)
Versus LMWH (standard dose; standard duration)	UFH (standard duration)	1.27 (0.95, 1.70)*	1.28 (0.72, 2.36)
	LMWH (standard dose) + AES	0.67 (0.32, 1.41)*	0.33 (0.10, 1.65)
	LMWH (high dose; standard duration)	0.40 (0.22, 0.72)*	0.61 (0.26, 1.28)
	IPCD	0.97 (0.37, 2.53)*	1.67 (0.77, 3.74)
	LMWH (standard dose; extended duration)	0.36 (0.23, 0.55)	0.41 (0.16, 0.95)
	Dabigatran	0.85 (0.66, 1.09)*	0.87 (0.30, 2.06)
	Foot pump	1.35 (0.77, 2.38)*	1.30 (0.29, 4.12)
	Apixaban	0.32 (0.20, 0.51)*	0.36 (0.07, 1.43)
	Rivaroxaban	0.20 (0.11, 0.35)*	0.14 (0.04, 0.51)
	VKA (standard duration)	0.57 (0.37, 0.86)*	0.94 (0.29, 2.52)
	UFH (extended duration)	-	1.97 (0.35, 7.54)
	Aspirin	-	1.15 (0.17, 4.55)
	LMWH (low dose) + AES	-	0.28 (0.04, 2.39)
	LMWH (extended duration) + AES	-	0.18 (0.02, 1.61)
	Fondaparinux + AES	-	0.14 (0.02, 1.31)
	AES (length unspecified)	-	0.66 (0.14, 4.01)
	LMWH (low dose; pre-op)	-	0.41 (0.05, 2.13)
	LMWH (low dose; post-op)	-	0.50 (0.07, 2.46)
	VKA (extended duration)	-	0.34 (0.03, 2.37)
	AES (above-knee)	-	0.50 (0.07, 5.45)
	LMWH (high dose) + AES	-	0.21 (0.02, 2.79)
	UFH + AES	-	0.58 (0.07, 4.94)
	Foot pump + AES	-	0.69 (0.08, 5.68)
	LMWH (high dose; extended duration)	-	0.25 (0.01, 2.65)
Versus UFH (standard duration)	LMWH (standard dose) + AES	-	0.25 (0.08, 1.32)
	LMWH (high dose; standard duration)	0.66 (0.50, 0.87)	0.48 (0.21, 0.94)
	IPCD	-	1.30 (0.54, 3.17)
	LMWH (standard dose; extended duration)	-	0.32 (0.10, 0.89)
	Dabigatran	-	0.68 (0.20, 1.88)
	Foot pump	-	1.03 (0.20, 3.55)
	Apixaban	-	0.28 (0.05, 1.25)
	Rivaroxaban	-	0.11 (0.03, 0.45)
	VKA (standard duration)	-	0.74 (0.20, 2.17)
	UFH (extended duration)	0.57 (0.18, 1.81)	1.53 (0.31, 5.36)
	Aspirin	4.17 (0.88, 19.66)*	0.90 (0.14, 3.17)
	LMWH (low dose) + AES	-	0.22 (0.03, 1.88)
	LMWH (extended duration) + AES	-	0.14 (0.02, 1.27)
	Fondaparinux + AES	-	0.11 (0.01, 1.02)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	AES (length unspecified)	-	0.51 (0.11, 3.17)
	LMWH (low dose; pre-op)	-	0.32 (0.04, 1.76)
	LMWH (low dose; post-op)	-	0.39 (0.03, 4.24)
	VKA (extended duration)	-	0.27 (0.02, 1.93)
	AES (above-knee)	-	0.39 (0.03, 4.24)
	LMWH (high dose) + AES	-	0.17 (0.01, 2.17)
	UFH + AES	-	0.45 (0.05, 3.89)
	Foot pump + AES	-	0.53 (0.06, 4.48)
	LMWH (high dose; extended duration)	-	0.20 (0.01, 2.16)
Versus LMWH (standard dose) + AES	LMWH (high dose; standard duration)	-	1.82 (0.28, 8.24)
	IPCD	-	5.36 (0.99, 13.82)
	LMWH (standard dose; extended duration)	-	1.21 (0.17, 6.59)
	Dabigatran	-	2.61 (0.36, 10.81)
	Foot pump	-	4.10 (0.43, 14.18)
	Apixaban	-	1.06 (0.10, 7.73)
	Rivaroxaban	-	0.42 (0.05, 3.30)
	VKA (standard duration)	-	2.85 (0.38, 11.60)
	UFH (extended duration)	-	6.67 (0.60, 16.55)
	Aspirin	-	3.54 (0.27, 14.52)
	LMWH (low dose) + AES	0.77 (0.48, 1.24)	0.84 (0.18, 3.53)
	LMWH (extended duration) + AES	0.61 (0.38, 0.97)	0.52 (0.10, 2.59)
	Fondaparinux + AES	0.44 (0.30, 0.64)*	0.43 (0.08, 2.03)
	AES (length unspecified)	1.58 (1.22, 2.06)*	2.00 (0.79, 4.61)
	LMWH (low dose; pre-op)	-	1.19 (0.08, 9.72)
	LMWH (low dose; post-op)	-	1.49 (0.11, 10.76)
	VKA (extended duration)	-	1.00 (0.05, 10.12)
	AES (above-knee)	-	1.51 (0.16, 8.73)
	LMWH (high dose) + AES	-	0.63 (0.06, 4.95)
	UFH + AES	-	1.74 (0.29, 7.26)
	Foot pump + AES	-	2.07 (0.36, 8.34)
	LMWH (high dose; extended duration)	-	0.74 (0.02, 10.73)
Versus LMWH (high dose; standard duration)	IPCD	-	2.76 (1.01, 8.59)
	LMWH (standard dose; extended duration)	-	0.68 (0.20, 2.20)
	Dabigatran	-	1.41 (0.40, 4.90)
	Foot pump	-	2.10 (0.41, 9.28)
	Apixaban	-	0.60 (0.10, 3.03)
	Rivaroxaban	-	0.24 (0.05, 1.03)
	VKA (standard duration)	1.35 (0.70, 2.61)*	1.53 (0.40, 5.64)
	UFH (extended duration)	-	3.18 (0.58, 15.07)
	Aspirin	-	1.83 (0.28, 8.93)
	LMWH (low dose) + AES	-	0.47 (0.05, 4.83)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (extended duration) + AES	-	0.29 (0.03, 3.28)
	Fondaparinux + AES	-	0.24 (0.02, 2.66)
	AES (length unspecified)	-	1.10 (0.18, 8.35)
	LMWH (low dose; pre-op)	-	0.67 (0.08, 4.33)
	LMWH (low dose; post-op)	-	0.83 (0.10, 5.05)
	VKA (extended duration)	-	0.57 (0.04, 4.71)
	AES (above-knee)	-	0.83 (0.05, 10.87)
	LMWH (high dose) + AES	-	0.36 (0.02, 5.52)
	UFH + AES	-	0.96 (0.09, 9.94)
	Foot pump + AES	-	1.14 (0.11, 11.68)
	LMWH (high dose; extended duration)	-	0.42 (0.02, 5.12)
Versus IPCD	LMWH (standard dose; extended duration)	-	0.25 (0.07, 0.79)
	Dabigatran	-	0.52 (0.14, 1.62)
	Foot pump	-	0.79 (0.14, 2.94)
	Apixaban	-	0.21 (0.03, 1.05)
	Rivaroxaban	-	0.08 (0.02, 0.39)
	VKA (standard duration)	1.00 (0.47, 2.11)*	0.56 (0.17, 1.48)
	UFH (extended duration)	-	1.19 (0.19, 4.86)
	Aspirin	-	0.69 (0.09, 3.01)
	LMWH (low dose) + AES	-	0.17 (0.02, 1.43)
	LMWH (extended duration) + AES	-	0.10 (0.01, 0.98)
	Fondaparinux + AES	-	0.08 (0.01, 0.79)
	AES (length unspecified)	-	0.38 (0.09, 2.44)
	LMWH (low dose; pre-op)	-	0.24 (0.03, 1.27)
	LMWH (low dose; post-op)	-	0.30 (0.04, 1.46)
	VKA (extended duration)	-	0.20 (0.02, 1.39)
	AES (above-knee)	-	0.30 (0.02, 3.21)
	LMWH (high dose) + AES	-	0.13 (0.01, 1.65)
	UFH + AES	-	0.34 (0.04, 2.95)
	Foot pump + AES	-	0.40 (0.05, 3.44)
	LMWH (high dose; extended duration)	-	0.15 (0.01, 1.55)
Versus LMWH (standard dose; extended duration)	Dabigatran	-	2.06 (0.56, 7.82)
	Foot pump	-	3.07 (0.59, 14.78)
	Apixaban	-	0.87 (0.14, 4.73)
	Rivaroxaban	0.22 (0.12, 0.41)*	0.35 (0.10, 1.18)
	VKA (standard duration)	-	2.24 (0.55, 9.29)
	UFH (extended duration)	-	4.68 (0.74, 26.51)
	Aspirin	-	2.67 (0.35, 15.99)
	LMWH (low dose) + AES	-	0.70 (0.07, 7.90)
	LMWH (extended duration) + AES	-	0.43 (0.04, 5.27)
	Fondaparinux + AES	-	0.36 (0.03, 4.31)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	AES (length unspecified)	-	1.64 (0.24, 13.76)
	LMWH (low dose; pre-op)	-	0.98 (0.11, 6.93)
	LMWH (low dose; post-op)	-	1.21 (0.14, 8.14)
	VKA (extended duration)	-	0.83 (0.06, 7.45)
	AES (above-knee)	-	1.23 (0.07, 17.59)
	LMWH (high dose) + AES	-	0.52 (0.03, 8.87)
	UFH + AES	-	1.42 (0.12, 16.35)
	Foot pump + AES	-	1.68 (0.15, 18.95)
	LMWH (high dose; extended duration)	-	0.62 (0.03, 8.12)
Versus Dabigatran	Foot pump	-	1.49 (0.27, 7.25)
	Apixaban	-	0.42 (0.06, 2.34)
	Rivaroxaban	-	0.17 (0.03, 0.82)
	VKA (standard duration)	-	1.09 (0.25, 4.63)
	UFH (extended duration)	-	2.24 (0.35, 13.01)
	Aspirin	-	1.31 (0.16, 7.71)
	LMWH (low dose) + AES	-	0.33 (0.04, 3.71)
	LMWH (extended duration) + AES	-	0.21 (0.02, 2.50)
	Fondaparinux + AES	-	0.17 (0.02, 2.00)
	AES (length unspecified)	-	0.77 (0.14, 6.46)
	LMWH (low dose; pre-op)	-	0.48 (0.05, 3.38)
	LMWH (low dose; post-op)	-	0.59 (0.04, 8.23)
	VKA (extended duration)	-	0.40 (0.03, 3.63)
	AES (above-knee)	-	0.59 (0.04, 8.28)
	LMWH (high dose) + AES	-	0.25 (0.02, 4.14)
	UFH + AES	-	0.68 (0.07, 7.66)
	Foot pump + AES	-	0.80 (0.08, 8.80)
	LMWH (high dose; extended duration)	-	0.30 (0.01, 3.96)
Versus Foot pump	Apixaban	-	0.28 (0.04, 2.07)
	Rivaroxaban	-	0.11 (0.02, 0.74)
	VKA (standard duration)	-	0.73 (0.14, 4.23)
	UFH (extended duration)	-	1.49 (0.20, 11.19)
	Aspirin	-	0.88 (0.10, 6.72)
	LMWH (low dose) + AES	-	0.22 (0.03, 2.93)
	LMWH (extended duration) + AES	-	0.14 (0.01, 1.97)
	Fondaparinux + AES	-	0.11 (0.01, 1.58)
	AES (length unspecified)	-	0.50 (0.10, 5.34)
	LMWH (low dose; pre-op)	-	0.32 (0.03, 2.84)
	LMWH (low dose; post-op)	-	0.40 (0.04, 3.41)
	VKA (extended duration)	-	0.27 (0.02, 3.07)
	AES (above-knee)	-	0.39 (0.03, 6.37)
	LMWH (high dose) + AES	-	0.17 (0.01, 3.15)
	UFH + AES	-	0.44 (0.05, 6.03)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	Foot pump + AES	-	0.52 (0.06, 7.07)
	LMWH (high dose; extended duration)	-	0.20 (0.01, 3.16)
Versus Apixaban	Rivaroxaban	-	0.40 (0.06, 3.02)
	VKA (standard duration)	-	2.57 (0.43, 17.96)
	UFH (extended duration)	-	5.35 (0.64, 48.48)
	Aspirin	-	3.04 (0.30, 28.57)
	LMWH (low dose) + AES	-	0.80 (0.06, 12.74)
	LMWH (extended duration) + AES	-	0.50 (0.04, 8.55)
	Fondaparinux + AES	-	0.41 (0.03, 6.87)
	AES (length unspecified)	-	1.88 (0.21, 23.11)
	LMWH (low dose; pre-op)	-	1.13 (0.09, 11.98)
	LMWH (low dose; post-op)	-	1.38 (0.12, 14.17)
	VKA (extended duration)	-	0.95 (0.05, 12.43)
	AES (above-knee)	-	1.41 (0.07, 28.04)
	LMWH (high dose) + AES	-	0.61 (0.03, 13.84)
	UFH + AES	-	1.63 (0.11, 26.26)
	Foot pump + AES	-	1.92 (0.14, 30.62)
	LMWH (high dose; extended duration)	-	0.71 (0.02, 12.98)
Versus Rivaroxaban	VKA (standard duration)	-	6.41 (1.23, 35.36)
	UFH (extended duration)	-	13.43 (1.70, 96.91)
	Aspirin	-	7.61 (0.84, 58.00)
	LMWH (low dose) + AES	-	2.01 (0.15, 27.57)
	LMWH (extended duration) + AES	-	1.26 (0.09, 18.53)
	Fondaparinux + AES	-	1.03 (0.07, 14.83)
	AES (length unspecified)	-	4.78 (0.50, 49.19)
	LMWH (low dose; pre-op)	-	2.79 (0.27, 24.81)
	LMWH (low dose; post-op)	-	3.42 (0.34, 29.03)
	VKA (extended duration)	-	2.35 (0.15, 26.30)
	AES (above-knee)	-	3.55 (0.17, 60.68)
	LMWH (high dose) + AES	-	1.52 (0.07, 30.36)
	UFH + AES	-	4.11 (0.27, 56.89)
	Foot pump + AES	-	4.83 (0.34, 66.14)
	LMWH (high dose; extended duration)	-	1.75 (0.07, 27.90)
Versus VKA (standard duration)	UFH (extended duration)	-	2.06 (0.31, 12.35)
	Aspirin	-	1.20 (0.14, 7.43)
	LMWH (low dose) + AES	-	0.30 (0.03, 3.47)
	LMWH (extended duration) + AES	-	0.19 (0.02, 2.32)
	Fondaparinux + AES	-	0.15 (0.02, 1.87)
	AES (length unspecified)	-	0.71 (0.13, 6.14)
	LMWH (low dose; pre-op)	0.45 (0.31, 0.64)	0.44 (0.09, 1.64)
	LMWH (low dose; post-op)	0.55 (0.39, 0.76)	0.54 (0.11, 1.91)
	VKA (extended duration)	0.36 (0.10, 1.33)	0.37 (0.04, 1.94)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	AES (above-knee)	-	0.54 (0.04, 7.78)
	LMWH (high dose) + AES	-	0.23 (0.01, 3.87)
	UFH + AES	-	0.62 (0.06, 7.21)
	Foot pump + AES	-	0.74 (0.07, 8.33)
	LMWH (high dose; extended duration)	0.74 (0.38, 1.44)	0.28 (0.02, 2.29)
Versus UFH (extended duration)	Aspirin	-	0.59 (0.06, 4.37)
	LMWH (low dose) + AES	-	0.14 (0.02, 1.98)
	LMWH (extended duration) + AES	-	0.09 (0.01, 1.33)
	Fondaparinux + AES	-	0.07 (0.01, 1.09)
	AES (length unspecified)	-	0.31 (0.07, 3.72)
	LMWH (low dose; pre-op)	-	0.21 (0.02, 2.09)
	LMWH (low dose; post-op)	-	0.26 (0.02, 2.48)
	VKA (extended duration)	-	0.18 (0.01, 2.13)
	AES (above-knee)	-	0.25 (0.02, 4.28)
	LMWH (high dose) + AES		0.11 (0.01, 2.13)
	UFH + AES	-	0.29 (0.03, 4.15)
	Foot pump + AES	-	0.34 (0.04, 4.88)
	LMWH (high dose; extended duration)	-	0.13 (0.00, 2.17)
Versus Aspirin	LMWH (low dose) + AES	-	0.25 (0.03, 4.42)
	LMWH (extended duration) + AES	-	0.16 (0.01, 2.93)
	Fondaparinux + AES	-	0.13 (0.01, 2.36)
	AES (length unspecified)	-	0.57 (0.10, 8.17)
	LMWH (low dose; pre-op)	-	0.37 (0.03, 4.39)
	LMWH (low dose; post-op)	-	0.46 (0.04, 5.28)
	VKA (extended duration)	-	0.31 (0.02, 4.50)
	AES (above-knee)	-	0.45 (0.03, 9.51)
	LMWH (high dose) + AES	-	0.19 (0.01, 4.71)
	UFH + AES	-	0.51 (0.05, 9.06)
	Foot pump + AES	-	0.60 (0.06, 10.77)
	LMWH (high dose; extended duration)	-	0.23 (0.01, 4.53)
Versus LMWH (low dose) + AES	LMWH (extended duration) + AES	-	0.62 (0.07, 5.81)
	Fondaparinux + AES	-	0.51 (0.06, 4.65)
	AES (length unspecified)	1.61 (1.04, 2.52)	2.35 (0.56, 10.69)
	LMWH (low dose; pre-op)	-	1.41 (0.07, 19.95)
	LMWH (low dose; post-op)	-	1.75 (0.09, 22.86)
	VKA (extended duration)	-	1.18 (0.04, 19.61)
	AES (above-knee)	1.45 (1.00, 2.11)	1.75 (0.35, 7.07)
	LMWH (high dose) + AES	-	0.75 (0.05, 9.99)
	UFH + AES	-	2.04 (0.26, 14.28)
	Foot pump + AES	-	2.40 (0.32, 16.79)
	LMWH (high dose; extended duration)	-	0.87 (0.02, 19.76)
Versus LMWH	Fondaparinux + AES	-	0.81 (0.08, 8.23)

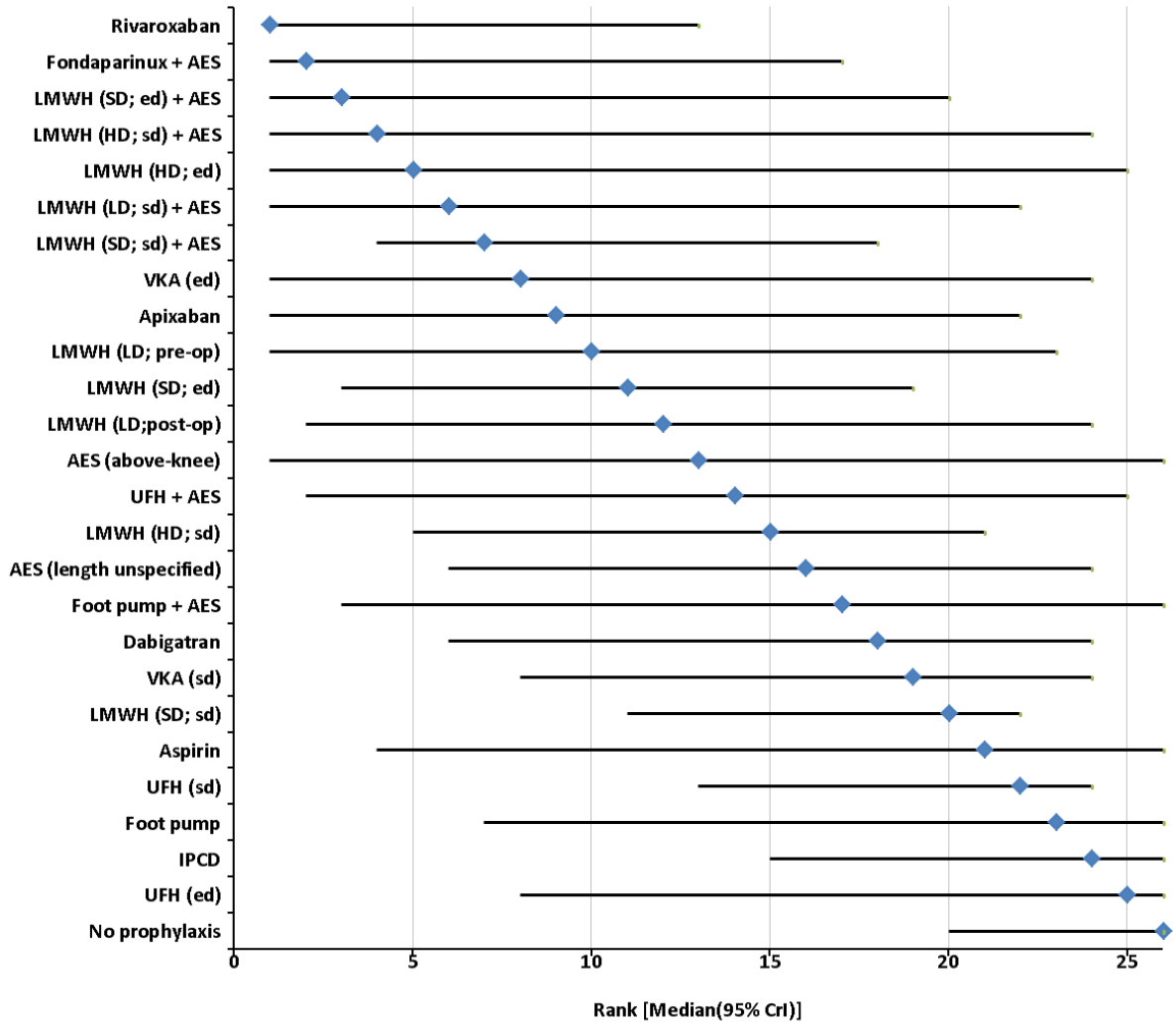
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
(standard dose; extended duration) + AES	AES (length unspecified)	-	3.80 (0.60, 25.16)
	LMWH (low dose; pre-op)	-	2.25 (0.11, 35.36)
	LMWH (low dose; post-op)	-	2.78 (0.13, 40.08)
	VKA (extended duration)	-	1.89 (0.06, 35.03)
	AES (above-knee)	-	2.84 (0.18, 33.96)
	LMWH (high dose) + AES	-	1.20 (0.07, 17.55)
	UFH + AES	-	3.28 (0.30, 30.52)
	Foot pump + AES	-	3.88 (0.37, 35.78)
	LMWH (high dose; extended duration)	-	1.39 (0.03, 35.31)
Versus fondaparinux + AES	AES (length unspecified)	-	4.65 (0.76, 29.22)
	LMWH (low dose; pre-op)	-	2.76 (0.13, 41.55)
	LMWH (low dose; post-op)	-	3.41 (0.16, 47.41)
	VKA (extended duration)	-	2.30 (0.08, 41.24)
	AES (above-knee)	-	3.46 (0.22, 39.92)
	LMWH (high dose) + AES	1.46 (1.01, 2.11)	1.47 (0.29, 6.50)
	UFH + AES	-	4.04 (0.38, 35.80)
	Foot pump + AES	-	4.75 (0.47, 41.79)
	LMWH (high dose; extended duration)	-	1.70 (0.04, 41.28)
Versus AES (length unspecified)	LMWH (low dose; pre-op)	-	0.60 (0.04, 6.00)
	LMWH (low dose; post-op)	-	0.74 (0.05, 6.71)
	VKA (extended duration)	-	0.50 (0.02, 6.09)
	AES (above-knee)	-	0.76 (0.08, 4.60)
	LMWH (high dose) + AES	-	0.32 (0.03, 3.00)
	UFH + AES	1.46 (1.01, 2.11)	0.87 (0.20, 3.00)
	Foot pump + AES	0.26 (0.09, 0.70)	1.03 (0.24, 3.48)
	LMWH (high dose; extended duration)	-	0.37 (0.01, 6.24)
Versus LMWH (low dose; standard duration; pre-op)	LMWH (low dose; post-op)	1.23 (0.81, 1.85)*	1.22 (0.28, 5.44)
	VKA (extended duration)	-	0.85 (0.07, 8.65)
	AES (above-knee)	-	1.25 (0.06, 31.23)
	LMWH (high dose) + AES	-	0.54 (0.02, 15.05)
	UFH + AES	-	1.45 (0.09, 29.53)
	Foot pump + AES	-	1.70 (0.11, 34.69)
	LMWH (high dose; extended duration)	-	0.64 (0.03, 9.39)
Versus LMWH (low dose; standard duration; post-op)	VKA (extended duration)	-	0.70 (0.06, 6.90)
	AES (above-knee)	-	1.01 (0.05, 24.79)
	LMWH (high dose) + AES	-	0.44 (0.02, 11.93)
	UFH + AES	-	1.17 (0.08, 23.26)
	Foot pump + AES	-	1.38 (0.10, 27.44)
	LMWH (high dose; extended duration)	-	0.52 (0.02, 7.44)
Versus VKA (extended duration)	AES (above-knee)	-	1.48 (0.06, 50.45)
	LMWH (high dose) + AES	-	0.65 (0.02, 24.76)
	UFH + AES	-	1.73 (0.09, 49.88)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	Foot pump + AES	-	2.03 (0.11, 58.64)
	LMWH (high dose; extended duration)	0.74 (0.38, 1.44)	0.76 (0.14, 3.29)
Versus AES (above-knee)	LMWH (high dose) + AES	-	0.43 (0.02, 8.95)
	UFH + AES	-	1.15 (0.11, 14.62)
	Foot pump + AES	-	1.36 (0.13, 17.26)
	LMWH (high dose; extended duration)	-	0.50 (0.01, 17.17)
Versus LMWH (high dose + AES)	UFH + AES	-	2.72 (0.18, 40.86)
	Foot pump + AES	-	3.20 (0.22, 48.42)
	LMWH (high dose; extended duration)	-	1.16 (0.02, 42.98)
Versus UFH + AES	Foot pump + AES	0.38 (0.19, 0.76)	1.18 (0.32, 4.50)
	LMWH (high dose; extended duration)	-	0.43 (0.01, 11.02)
Versus Foot pump + AES	LMWH (high dose; extended duration)	-	0.37 (0.01, 8.98)

**Intervention and comparison numbers have been switched in Review Manager*

Figure 828 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 26 different interventions being evaluated.

Figure 828: Rank order for interventions based the relative risk of experiencing DVT



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 570 compared with 634 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 90 reported. This corresponds well to the total number of trial arms, 88. The between trial standard deviation in the random effects analysis was 0.78 (95% CI 0.52 to 1.16). On evaluating inconsistency by comparing risk ratios, eight inconsistencies were identified. The NMA estimated risk ratio for:

- LMWH at a standard dose for a standard duration plus AES versus no prophylaxis (0.14 [0.07, 0.59]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.27 [0.15, 0.50])
- IPCD versus no prophylaxis (0.80 [0.34, 1.41]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.53 [0.40, 0.69])
- VKA at a standard duration versus LMWH at a standard dose and standard duration (0.94 [0.29, 2.52]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.57 [0.37, 0.86])
- LMWH at a high dose and standard duration versus UFH (0.48 [0.21, 0.94]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.66 [0.50, 0.87])

- LMWH at a high dose and extended duration versus VKA at a standard duration (0.28 [0.02, 2.29]) lay outside of the confidence interval of the risk ration estimated for the direct comparison (0.74 [0.38, 1.44])
- Foot pump plus AES (length unspecified) versus AES (length unspecified) (1.03 [0.24, 3.48]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.26 [0.09, 0.70])
- UFH plus AES (length unspecified) versus AES (length unspecified) (0.87 [0.20, 3.00]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (1.46 [1.01, 2.11])
- Foot pump plus AES (length unspecified) versus UFH plus AES (length unspecified) (1.18 [0.32, 4.50]) lay outside of the confidence interval of the risk ration estimated for the direct comparison (0.38 [0.19, 0.76])

An inconsistency model was run and the DIC statistics were as follows in **Table 240**. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 240: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – DVT

	DIC	ResDev
Consistency model	570.092	90
Inconsistency model	570.268	90

M.1.3.2 Pulmonary embolism

Included studies

37 studies were identified as reporting on PE outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 30 studies involving 23 treatments were included in the network for PE. The network can be seen in **Figure 829** and the trial data for each of the studies included in the NMA are presented in **Table 241**.

Figure 829: Network diagram for PE

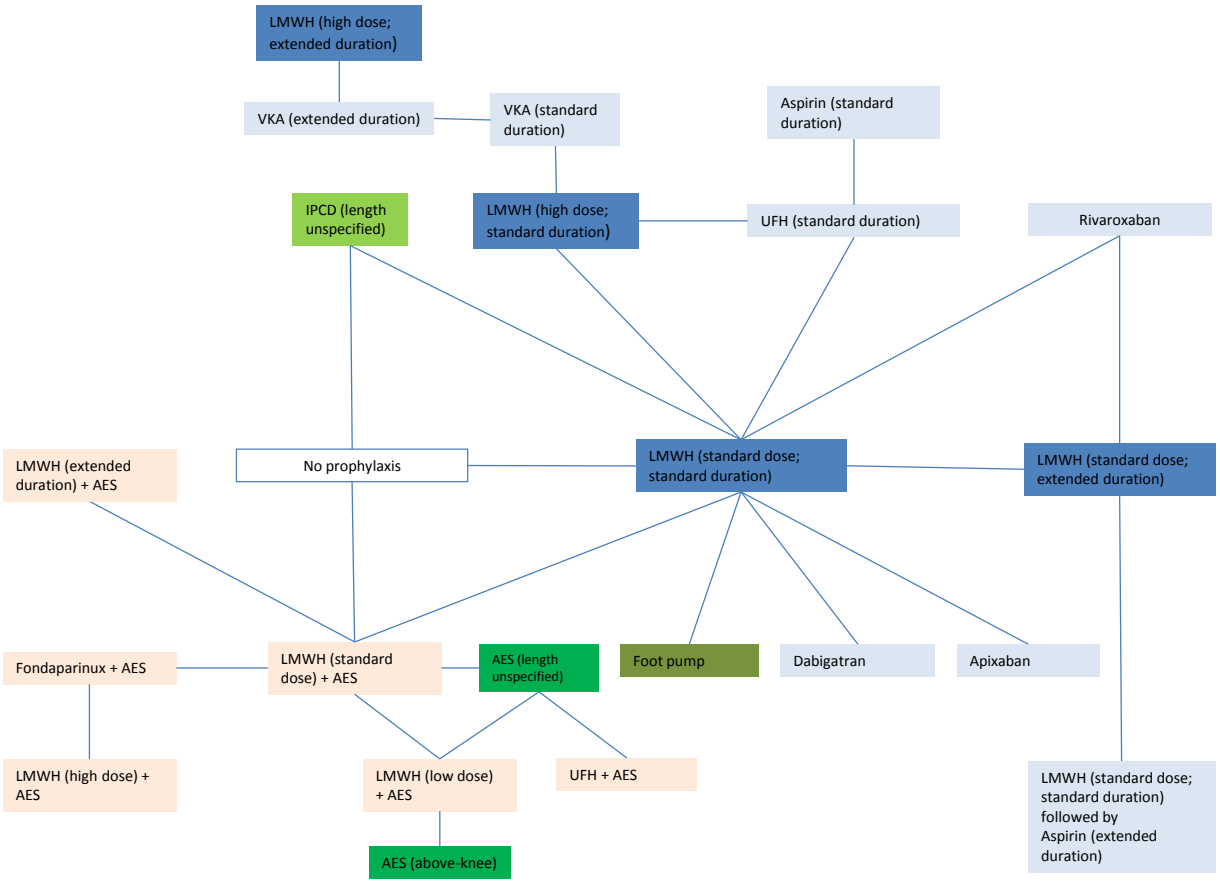


Table 241: Study data for PE network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
				N	NA	N	NA	N	NA
Kalodiki 1996 [472]	No prophylaxis	LMWH (standard dose; standard duration)	LMWH (standard dose) + AES	5	14	3	32	2	32
Bergqvist 1996 [92]	No prophylaxis	LMWH (standard dose; standard duration)	-	2	116	0	117	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
Torholm 1991 [941]	No prophylaxis	LMWH (standard dose; standard duration)	-	1	54	0	58	-	-
Hull 1990 [441]	No prophylaxis	IPCD (length unspecified)	-	1	158	1	152	-	-
Hardwick 2011 [389]	LMWH (standard dose; standard duration)	IPCD (length unspecified)	-	2	196	2	194	-	-
Avikainen 1995 [57]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	0	84	1	83	-	-
Colwell 1994 [204]	LMWH (standard dose; standard duration)	UFH (standard duration)	LMWH (high dose; standard duration)	1	203	4	209	0	195
Eriksson 1991A[289]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	1	67	2	69	-	-
Planès 1990 [758]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	0	120	1	106	-	-
Comp 2001 [208]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	1	211	0	224	-	-
Eriksson 2011 [292]	LMWH (standard dose; standard duration)	Dabigatran	-	2	992	1	1001	-	-
Eriksson 2007 [288]	LMWH (standard dose; standard duration)	Dabigatran	-	3	897	5	880	-	-
Warwick 1998 [994]	LMWH (standard dose; standard duration)	Foot pump	-	0	138	1	136	-	-
Lassen 2010 [534]	LMWH (standard dose; standard duration)	Apixaban	-	5	2699	3	2708	-	-
Kakkar 2008 [467]	LMWH (standard dose; standard duration)	Rivaroxaban	-	4	869	1	864	-	-
Dahl 1997 [227]	LMWH (standard dose)	LMWH (extended	-	3	106	0	111	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
	+ AES	duration) + AES							
Lassen 2002 [526]	LMWH (standard dose) + AES	Fondaparinux + AES	-	3	1123	3	1129	-	-
Fuji 2008A [328]	LMWH (standard dose) + AES	LMWH (low dose) + AES	AES (length unspecified)	1	80	0	81	0	86
Warwick 1995A [992]	LMWH (standard dose) + AES	AES (length unspecified)	-	1	78	2	78	-	-
Kakkar 2000 [468]	LMWH (high dose; standard duration)	UFH (standard duration)	-	1	125	2	134	-	-
Levine 1991 [551]	LMWH (high dose; standard duration)	UFH (standard duration)	-	1	332	1	333	-	-
Colwell 1999 [203]	LMWH (high dose; standard duration)	VKA (standard duration)	-	6	1516	9	1495	-	-
Samama 2002 [845]	LMWH (high dose; extended duration)	VKA (extended duration)	-	0	643	4	636	-	-
Zanasi 1988 [1039]	UFH (standard duration)	Aspirin (standard duration)	-	1	25	1	19	-	-
Eriksson 2008 [291]	LMWH (standard dose; extended duration)	Rivaroxaban	-	1	1558	4	1595	-	-
Anderson 2013 [40]	LMWH (standard dose; extended duration)	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	3	398	0	380	-	-
Turpie 2002K [954]	Fondaparinux + AES	LMWH (high dose) + AES	-	5	1126	0	1128	-	-
Moskovtiz 1978 [657]	AES (length unspecified)	UFH + AES	-	1	32	3	35	-	-
Lassen 1991 [529]	LMWH (low dose) + AES	AES (above-knee)	-	2	93	1	97	-	-
Prandoni 2002 [771]	VKA (standard duration)	VKA (extended duration)	-	1	176	0	184	-	-

N; number of events, NA; number analysed

NMA results

Table 242 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 242: Risk ratios for PE

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	LMWH (standard dose; standard duration)	0.15 (0.04, 0.58)	0.25 (0.06, 0.89)
	LMWH (standard dose) + AES	0.17 (0.04, 0.80)	0.12 (0.02, 0.82)
	IPCD (length unspecified)	1.04 (0.07, 16.47)	0.41 (0.05, 2.97)
	UFH (standard duration)	-	0.65 (0.10, 4.02)
	Rivaroxaban	-	0.07 (0.00, 0.78)
	LMWH (standard dose; extended duration)	-	0.02 (0.00, 0.34)
	LMWH (high dose; standard duration)	-	0.21 (0.02, 2.09)
	Dabigatran	-	0.29 (0.04, 1.87)
	Foot pump	-	1.18 (0.03, 29.88)
	Apixaban	-	0.14 (0.01, 1.21)
	AES (length unspecified)	-	0.12 (0.01, 2.08)
	LMWH (low dose) + AES	-	0.03 (0.00, 1.87)
	Fondaparinux + AES	-	0.12 (0.01, 1.95)
	LMWH (extended duration) + AES	-	0.01 (0.00, 0.31)
	Aspirin (standard duration)	-	3.43 (0.09, 45.71)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.10)
	VKA (standard duration)	-	0.33 (0.02, 4.32)
	UFH + AES	-	0.45 (0.01, 18.78)
	AES (above-knee)	-	0.17 (0.00, 24.69)
	LMWH (high dose) + AES	-	0.00 (0.00, 0.30)
	VKA (extended duration)		0.06 (0.00, 4.46)
	LMWH (high dose; extended duration)		0.00 (0.00, 0.81)
Versus LMWH (standard dose; standard duration)	LMWH (standard dose) + AES	0.67 (0.12, 3.73)	0.52 (0.05, 3.82)
	IPCD (length unspecified)	1.01 (0.14, 7.10)*	1.63 (0.23, 11.08)
	UFH (standard duration)	3.01 (0.82,11.03)*	2.60 (0.73, 10.33)
	Rivaroxaban	0.25 (0.03, 2.25)*	0.29 (0.02, 2.14)
	LMWH (standard dose; extended duration)	0.30 (0.01, 7.37)	0.08 (0.00, 1.00)
	LMWH (high dose; standard duration)	0.35 (0.01, 8.47)	0.87 (0.11, 5.55)
	Dabigatran	1.21 (0.37, 3.96)*	1.19 (0.27, 4.76)
	Foot pump	-	4.51 (0.15, 118.90)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	Apixaban	0.60 (0.14, 2.50)*	0.57 (0.08, 3.18)
	AES (length unspecified)	-	0.49 (0.02, 9.58)
	LMWH (low dose) + AES	-	0.14 (0.00, 8.53)
	Fondaparinux + AES	0.25 (0.03, 2.25)*	0.51 (0.03, 8.51)
	LMWH (extended duration) + AES	-	0.03 (0.00, 1.41)
	Aspirin (standard duration)	-	13.34 (0.44, 181.20)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.33)
	VKA (standard duration)	-	1.34 (0.11, 12.45)
	UFH + AES	-	1.88 (0.03, 83.70)
	AES (above-knee)	-	0.69 (0.00, 109.60)
	LMWH (high dose) + AES	-	0.02 (0.00, 1.26)
	VKA (extended duration)	-	0.25 (0.00, 14.26)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 2.76)
Versus LMWH (standard dose; standard duration) + AES	IPCD (length unspecified)	-	3.22 (0.22, 45.98)
	UFH (standard duration)	-	5.30 (0.48, 54.12)
	Rivaroxaban	-	0.53 (0.02, 11.48)
	LMWH (standard dose; extended duration)	-	0.15 (0.00, 4.70)
	LMWH (high dose; standard duration)	0.97 (0.17, 5.47)*	1.71 (0.09, 28.52)
	Dabigatran	-	2.32 (0.19, 29.85)
	Foot pump	-	10.44 (0.16, 143.60)
	Apixaban	-	1.10 (0.07, 18.05)
	AES (length unspecified)	0.97 (0.17, 21.61)*	0.97 (0.11, 8.04)
	LMWH (low dose) + AES	0.33 (0.01, 7.96)	0.29 (0.00, 9.28)
	Fondaparinux + AES	-	1.00 (0.13, 7.52)
	LMWH (extended duration) + AES	-	0.07 (0.00, 1.37)
	Aspirin (standard duration)	-	34.54 (0.52, 148.70)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 1.13)
	VKA (standard duration)	-	2.66 (0.10, 50.54)
	UFH + AES	-	3.64 (0.13, 90.72)
	AES (above-knee)	-	1.38 (0.00, 128.90)
	LMWH (high dose) + AES	-	0.04 (0.00, 1.49)
	VKA (extended duration)	-	0.47 (0.00, 48.12)
	LMWH (high dose; extended duration)	-	0.02 (0.00, 8.29)
Versus IPCD	UFH (standard duration)	-	1.61 (0.16, 16.85)
	Rivaroxaban	-	0.17 (0.01, 2.96)
	LMWH (standard dose; extended	-	0.05 (0.00, 1.21)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	duration)		
	LMWH (high dose; standard duration)	-	0.54 (0.03, 7.90)
	Dabigatran	-	0.73 (0.06, 7.96)
	Foot pump	-	2.88 (0.05, 123.10)
	Apixaban	-	0.35 (0.02, 4.70)
	AES (length unspecified)	-	0.30 (0.01, 9.30)
	LMWH (low dose) + AES	-	0.08 (0.00, 7.49)
	Fondaparinux + AES	-	0.31 (0.01, 8.70)
	LMWH (extended duration) + AES	-	0.02 (0.00, 1.30)
	Aspirin (standard duration)	-	8.03 (0.16, 206.90)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.31)
	VKA (standard duration)	-	0.83 (0.04, 15.75)
	UFH + AES	-	1.16 (0.02, 74.21)
	AES (above-knee)	-	0.42 (0.00, 96.92)
	LMWH (high dose) + AES	-	0.01 (0.00, 1.17)
	VKA (extended duration)	-	0.15 (0.00, 14.26)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 2.22)
Versus UFH (standard duration)	Rivaroxaban	-	0.11 (0.01, 1.19)
	LMWH (standard dose; extended duration)	-	0.03 (0.00, 0.52)
	LMWH (high dose; standard duration)	0.35 (0.08, 1.47)	0.34 (0.05, 1.40)
	Dabigatran	-	0.45 (0.06, 2.97)
	Foot pump	-	1.77 (0.04, 56.95)
	Apixaban	-	0.21 (0.02, 1.85)
	AES (length unspecified)	-	0.18 (0.01, 4.70)
	LMWH (low dose) + AES	-	0.05 (0.00, 3.85)
	Fondaparinux + AES	-	0.19 (0.01, 4.11)
	LMWH (extended duration) + AES		0.01 (0.00, 0.65)
	Aspirin (standard duration)	2.88 (0.46, 18.06)*	4.66 (0.21, 75.89)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.15)
	VKA (standard duration)	-	0.52 (0.05, 3.60)
	UFH + AES	-	0.70 (0.01, 39.25)
	AES (above-knee)	-	0.26 (0.00, 48.78)
	LMWH (high dose) + AES	-	0.01 (0.00, 0.57)
	VKA (extended duration)		0.10 (0.00, 4.67)
	LMWH (high dose; extended duration)		0.00 (0.00, 0.92)
Versus	LMWH (standard dose; extended	0.31 (0.05, 1.78)	0.28 (0.02, 2.17)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Rivaroxaban	duration)		
	LMWH (high dose; standard duration)	-	3.06 (0.18, 75.17)
	Dabigatran	-	4.20 (0.33, 82.88)
	Foot pump	-	16.83 (0.30, 1021.00)
	Apixaban	-	2.01 (0.12, 45.80)
	AES (length unspecified)	-	1.81 (0.04, 86.58)
	LMWH (low dose) + AES	-	0.50 (0.00, 64.91)
	Fondaparinux + AES	-	1.88 (0.05, 79.40)
	LMWH (extended duration) + AES	-	0.11 (0.00, 11.74)
	Aspirin (standard duration)	-	47.43 (0.94, 1872.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.02 (0.00, 0.84)
	VKA (standard duration)	-	4.77 (0.20, 143.70)
	UFH + AES	-	6.97 (0.07, 664.60)
	AES (above-knee)	-	2.56 (0.00, 697.00)
	LMWH (high dose) + AES	-	0.07 (0.00, 9.59)
	VKA (extended duration)	-	0.88 (0.00, 113.30)
	LMWH (high dose; extended duration)	-	0.04 (0.00, 18.95)
Versus LMWH (standard dose; extended duration)	LMWH (high dose; standard duration)	-	11.42 (0.41, 493.60)
	Dabigatran	-	15.57 (0.77, 598.20)
	Foot pump	-	64.15 (0.82, 6018.00)
	Apixaban	-	7.48 (0.29, 311.80)
	AES (length unspecified)	-	6.64 (0.12, 558.20)
	LMWH (low dose) + AES	-	1.84 (0.00, 346.30)
	Fondaparinux + AES	3.91 (0.44, 34.92)*	6.99 (0.13, 512.20)
	LMWH (extended duration) + AES	-	0.40 (0.00, 63.43)
	Aspirin (standard duration)	-	175.90 (2.45, 12110.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	0.15 (0.01, 2.89)*	0.07 (0.00, 1.46)
	VKA (standard duration)	-	17.66 (0.48, 931.10)
	UFH + AES	-	25.95 (0.21, 4081.00)
	AES (above-knee)	-	9.84 (0.01, 3985.00)
	LMWH (high dose) + AES	-	0.27 (0.00, 54.28)
	VKA (extended duration)		3.27 (0.00, 650.10)
	LMWH (high dose; extended duration)		0.13 (0.00, 96.85)
Versus LMWH (high dose; standard	Dabigatran	-	1.36 (0.13, 16.37)
	Foot pump	-	5.31 (0.10, 274.50)
	Apixaban	-	0.65 (0.05, 9.72)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
duration)	AES (length unspecified)	-	0.57 (0.02, 20.87)
	LMWH (low dose) + AES	-	0.15 (0.00, 16.59)
	Fondaparinux + AES	-	0.59 (0.02, 18.62)
	LMWH (extended duration) + AES	-	0.04 (0.00, 2.89)
	Aspirin (standard duration)	-	14.19 (0.47, 387.50)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 0.62)
	VKA (standard duration)	0.66 (0.23, 1.84)	1.53 (0.37, 6.16)
	UFH + AES	-	2.22 (0.03, 162.40)
	AES (above-knee)	-	0.78 (0.00, 205.60)
	LMWH (high dose) + AES	-	0.02 (0.00, 2.37)
	VKA (extended duration)	-	0.30 (0.00, 10.82)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 2.07)
Versus Dabigatran	Foot pump	-	3.85 (0.10, 142.40)
	Apixaban	-	0.48 (0.04, 4.69)
	AES (length unspecified)	-	0.41 (0.02, 11.16)
	LMWH (low dose) + AES	-	0.11 (0.00, 9.14)
	Fondaparinux + AES	-	0.43 (0.02, 10.35)
	LMWH (extended duration) + AES	-	0.03 (0.00, 1.57)
	Aspirin (standard duration)	-	11.07 (0.29, 226.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.36)
	VKA (standard duration)	-	1.13 (0.07, 16.88)
	UFH + AES	-	1.60 (0.02, 92.90)
	AES (above-knee)	-	0.58 (0.00, 114.40)
	LMWH (high dose) + AES	-	0.02 (0.00, 1.42)
	VKA (extended duration)	-	0.21 (0.00, 16.13)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 2.81)
Versus Foot pump	Apixaban	-	0.12 (0.00, 5.59)
	AES (length unspecified)	-	0.09 (0.00, 9.71)
	LMWH (low dose) + AES	-	0.03 (0.00, 6.62)
	Fondaparinux + AES	-	0.10 (0.00, 9.98)
	LMWH (extended duration) + AES	-	0.01 (0.00, 1.18)
	Aspirin (standard duration)	-	2.49 (0.03, 224.30)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.26)
	VKA (standard duration)	-	0.29 (0.00, 17.57)
	UFH + AES	-	0.38 (0.00, 69.71)
	AES (above-knee)	-	0.14 (0.00, 78.93)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (high dose) + AES	-	0.00 (0.00, 1.08)
	VKA (extended duration)	-	0.05 (0.00, 12.09)
	LMWH (high dose; extended duration)	-	0.00 (0.00, 1.54)
Versus Apixaban	AES (length unspecified)	-	0.87 (0.03, 30.52)
	LMWH (low dose) + AES	-	0.24 (0.00, 23.71)
	Fondaparinux + AES	-	0.90 (0.03, 27.94)
	LMWH (extended duration) + AES	-	0.06 (0.00, 4.03)
	Aspirin (standard duration)	-	22.98 (0.56, 601.70)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 0.89)
	VKA (standard duration)	-	2.38 (0.12, 44.65)
	UFH + AES	-	3.36 (0.04, 231.40)
	AES (above-knee)	-	1.23 (0.00, 292.10)
	LMWH (high dose) + AES	-	0.04 (0.00, 3.49)
	VKA (extended duration)	-	0.43 (0.00, 37.71)
	LMWH (high dose; extended duration)	-	0.02 (0.00, 6.53)
Versus AES (length unspecified)	LMWH (low dose) + AES	-	0.30 (0.00, 9.69)
	Fondaparinux + AES	-	1.02 (0.06, 19.24)
	LMWH (extended duration) + AES	-	0.06 (0.00, 2.97)
	Aspirin (standard duration)	-	31.53 (0.32, 593.60)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 1.87)
	VKA (standard duration)	-	2.75 (0.06, 106.00)
	UFH + AES	2.74 (0.30, 25.05)	3.59 (0.30, 63.62)
	AES (above-knee)	-	1.43 (0.00, 186.90)
	LMWH (high dose) + AES	-	0.04 (0.00, 2.98)
	VKA (extended duration)	-	0.47 (0.00, 76.14)
	LMWH (high dose; extended duration)	-	0.02 (0.00, 11.98)
Versus LMWH (low dose) + AES	Fondaparinux + AES	-	3.57 (0.07, 1617.00)
	LMWH (extended duration) + AES	-	0.22 (0.00, 154.80)
	Aspirin (standard duration)	-	105.40 (0.46, 51270.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.03 (0.00, 53.02)
	VKA (standard duration)	-	10.18 (0.08, 5399.00)
	UFH + AES	-	13.70 (0.16, 8649.00)
	AES (above-knee)	1.00 (0.06, 15.76)	4.55 (0.14, 390.60)
	LMWH (high dose) + AES	-	0.14 (0.00, 130.20)
	VKA (extended duration)		1.71 (0.00, 2387.00)

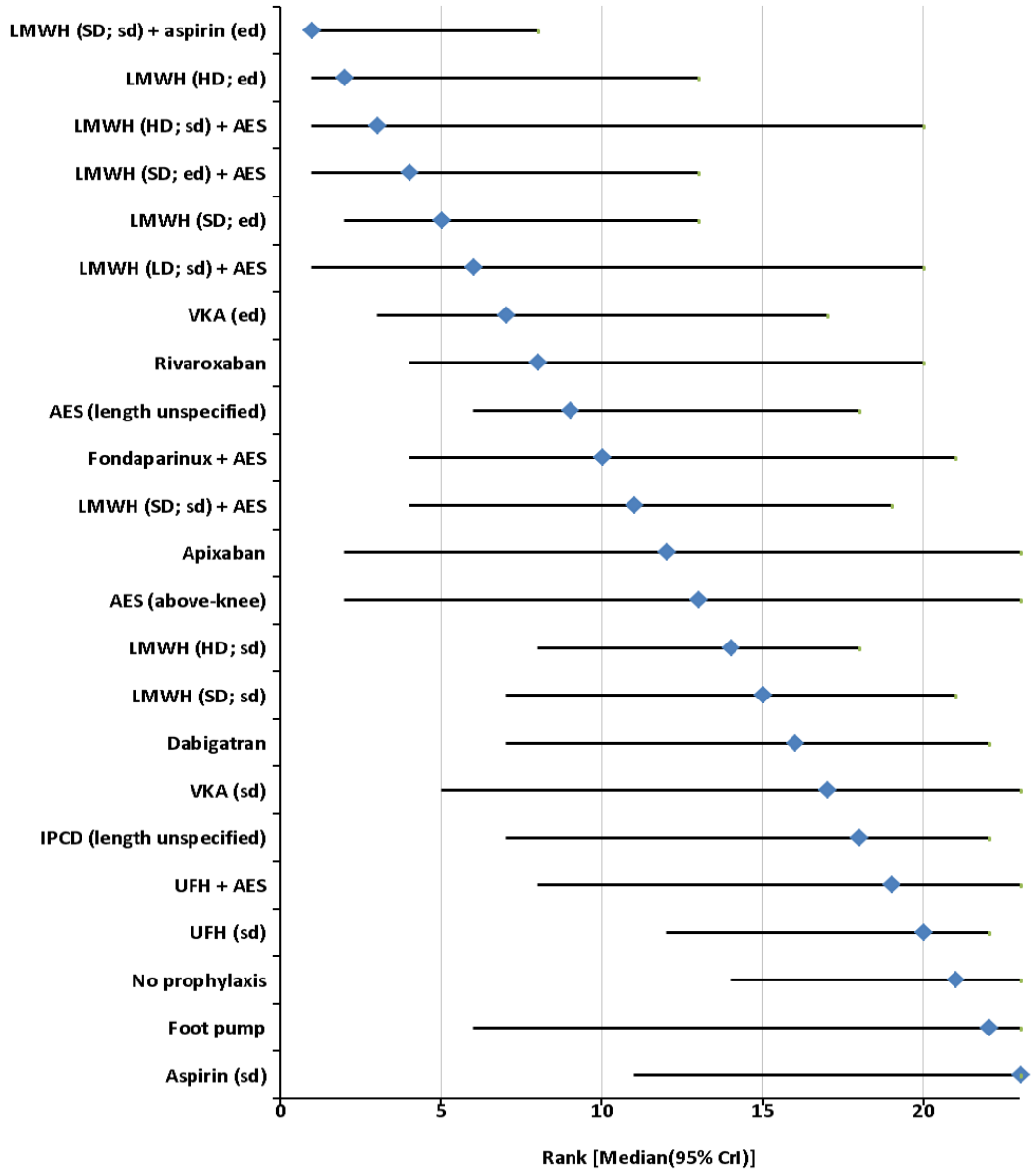
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (high dose; extended duration)		0.07 (0.00, 248.80)
Versus fondaparinux + AES	LMWH (extended duration) + AES	-	0.06 (0.00, 2.67)
	Aspirin (standard duration)	-	30.57 (0.33, 561.70)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 1.73)
	VKA (standard duration)	-	2.65 (0.06, 93.52)
	UFH + AES	-	3.69 (0.08, 153.80)
	AES (above-knee)	1.00 (0.06, 15.76)	1.38 (0.00, 216.10)
	LMWH (high dose) + AES	0.09 (0.01, 1.64)	0.05 (0.00, 0.76)
	VKA (extended duration)	-	0.46 (0.00, 70.47)
	LMWH (high dose; extended duration)	-	0.02 (0.00, 11.65)
Versus LMWH (standard dose; extended duration) + AES	Aspirin (standard duration)	-	464.20 (2.80, 242800.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.15 (0.00, 254.00)
	VKA (standard duration)	-	43.65 (0.43, 30520.00)
	UFH + AES	-	64.47 (0.55, 48030.00)
	AES (above-knee)	-	26.19 (0.01, 37000.00)
	LMWH (high dose) + AES	-	0.66 (0.00, 571.60)
	VKA (extended duration)	-	8.20 (0.00, 13090.00)
	LMWH (high dose; extended duration)	-	0.34 (0.00, 1307.00)
Versus aspirin (standard duration)	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.08)
	LMWH (high dose) + AES	-	0.11 (0.00, 4.01)
	UFH + AES	-	0.13 (0.00, 20.61)
	AES (above-knee)	-	0.05 (0.00, 24.21)
	VKA (standard duration)	-	0.00 (0.00, 0.32)
	VKA (extended duration)	-	0.02 (0.00, 2.85)
	LMWH (high dose; extended duration)	-	0.00 (0.00, 0.44)
Versus LMWH (standard dose; standard duration) + aspirin (extended duration)	LMWH (high dose) + AES	-	291.70 (2.02, 392100.00)
	UFH + AES	-	437.20 (1.06, 869900.00)
	AES (above-knee)	-	169.70 (0.05, 610700.00)
	VKA (standard duration)	-	4.35 (0.00, 11340.00)
	VKA (extended duration)	-	51.11 (0.02, 143200.00)
	LMWH (high dose; extended duration)	-	2.14 (0.00, 12350.00)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus LMWH (high dose) + AES	UFH + AES	-	1.43 (0.02, 133.70)
	AES (above-knee)	-	0.51 (0.00, 161.90)
	VKA (standard duration)	-	0.01 (0.00, 1.86)
	VKA (extended duration)	-	0.20 (0.00, 5.27)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 1.07)
Versus UFH + AES	AES (above-knee)	-	0.39 (0.00, 99.84)
	VKA (standard duration)	-	0.01 (0.00, 1.58)
	VKA (extended duration)	-	0.12 (0.00, 41.97)
	LMWH (high dose; extended duration)	-	0.00 (0.00, 5.61)
Versus AES (above-knee)	VKA (standard duration)	-	0.03 (0.00, 57.82)
	VKA (extended duration)	-	0.33 (0.00, 1053.00)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 100.60)
Versus VKA (standard duration)	VKA (extended duration)	0.32 (0.01, 7.78)	12.18 (0.01, 23630.00)
	LMWH (high dose; extended duration)	0.11 (0.01, 2.04)	0.54 (0.00, 2480.00)
Versus VKA (extended duration	LMWH (high dose; extended duration)	-	0.06 (0.00, 0.99)

**Intervention and comparison numbers have been switched in Review Manager*

Figure 830 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 23 different interventions being evaluated.

Figure 830: Rank order for interventions based the relative risk of experiencing PE



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 255 compared with 276 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 61 reported. This corresponds well to the total number of trial arms, 62. The between trial standard deviation in the random effects analysis was 0.41 (95% CI 0.14 to 1.04). On evaluating inconsistency by comparing risk ratios, one inconsistency was identified. The NMA estimated risk ratio for VKA at an extended duration versus VKA at a standard duration (12.18 [1.01, 23630.00]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.32 [0.01, 7.78]). An inconsistency model was run and the DIC statistics were as follows in Table 243. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 243: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – PE

	DIC	ResDev
Consistency model	255.025	61
Inconsistency model	258.386	63

M.1.3.3 Major bleeding

Included studies

28 studies were identified as reporting on major bleeding outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 24 studies involving 15 treatments were included in the network for PE. The network can be seen in **Figure 831** and the trial data for each of the studies included in the NMA are presented in

Table 244.

Figure 831: Network diagram for major bleeding

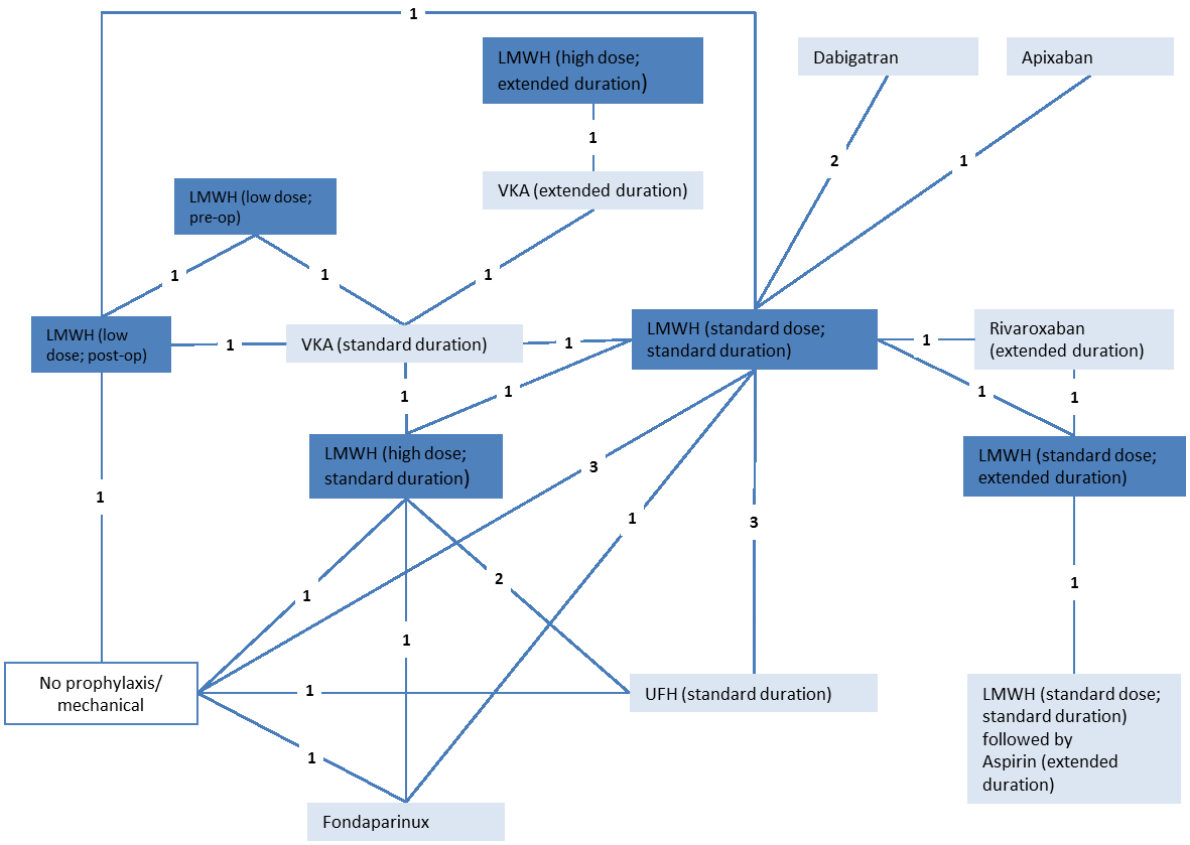


Table 244: Study data for major bleeding network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
				N	NA	N	NA	N	NA
Moskovitz 1978 [657]	No prophylaxis/ mechanical	UFH (standard duration)	-	3	35	0	32	-	-
Turpie 1986 [952]	No prophylaxis/ mechanical	LMWH (high dose; standard duration)	-	1	50	2	50	-	-
Fuji 2008A [328]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	LMWH (low dose; post-op)	0	101	2	102	1	100
Hardwick 2011 [389]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	-	0	198	11	194	-	-
Samama 1997 [844]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	-	1	75	1	78	-	-
Fuji 2008 [325]	No prophylaxis/ mechanical	Fondaparinux	-	0	82	2	81	-	-
Levine 1991 [551]	UFH (standard duration)	LMWH (high dose; standard duration)	-	19	332	11	333	-	-
Colwell 1994 [204]	UFH (standard duration)	LMWH (high dose; standard duration)	LMWH (standard dose; standard duration)	13	209	8	195	3	203
Eriksson 1991A [289]	UFH (standard duration)	LMWH (standard dose; standard duration)	-	5	69	1	67	-	-
Plànes 1990 [758]	UFH (standard duration)	LMWH (standard dose; standard duration)	-	0	106	2	120	-	-
Turpie 2002K[954]	LMWH (high dose; standard duration)	Fondaparinux	-	11	1129	20	1128	-	-
Colwell 1999 [203]	LMWH (high dose; standard duration)	VKA (standard duration)	-	6	1516	4	1495	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
Lassen 2002[526]	LMWH (standard dose; standard duration)	Fondaparinux	-	32	1133	47	1140	-	-
Francis 1997 [315]	LMWH (standard dose; standard duration)	VKA (standard duration)	-	6	271	4	279	-	-
Eriksson 2011 [292]	LMWH (standard dose; standard duration)	Dabigatran	-	9	1003	14	1010	-	-
Eriksson 2007 [288]	LMWH (standard dose; standard duration)	Dabigatran	-	18	1154	23	1146	-	-
Lassen 2010 [534]	LMWH (standard dose; standard duration)	Apixaban	-	18	2659	22	2673	-	-
Kakkar 2008 [467]	LMWH (standard dose; standard duration)	Rivaroxaban	-	19	1257	23	1252	-	-
Lassen 1998 [527]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	1	141	0	140	-	-
Hull 2000[440]	LMWH (low dose; post-op)	VKA (standard duration)	LMWH (low dose; pre-op)	32	487	22	489	44	496
Prandoni 2002 [771]	VKA (standard duration)	VKA (extended duration)	-	0	176	1	184	-	-
Eriksson 2008 [291]	LMWH (standard dose; extended duration)	Rivaroxaban	-	33	2225	40	2266	-	-
Anderson 2013 [40]	LMWH (standard dose; extended duration)	LMWH (st; st duration) + aspirin (extended)	-	1	400	0	386	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
Samama 2002 [845]	LMWH (high dose; extended duration)	VKA (extended duration)	-	10	643	37	636	-	-

N; number of events, NA; number analysed

NMA results

Table 245 summarises the results of the conventional meta-analyses in terms of odd ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of odd ratios for every possible treatment comparison. Relative risks were not calculated for this outcome as data was only available for non-surgical site bleeding (intracranial haemorrhage + gastrointestinal bleeding) from the observational study used as the source of baseline risk.[451]

Table 245: Odd ratios for major bleeding

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis/ mechanical	UFH (standard duration)	7.00 (0.35, 140.99)	3.58 (0.89, 13.67)
	LMWH (high dose; standard duration)	0.49 (0.04, 5.58)	2.47 (0.67, 9.56)
	LMWH (standard dose; standard duration)	7.66 (1.76, 33.31)	2.55 (0.82, 8.70)
	Fondaparinux	5.19 (0.25, 109.77)	4.28 (1.07, 18.66)
	LMWH (low dose; post-op)	3.06 (0.12, 76.02)	2.20 (0.35, 13.35)
	VKA (standard duration)	-	1.54 (0.31, 7.94)
	Dabigatran	-	3.63 (0.74, 18.48)
	Apixaban	-	3.16 (0.47, 21.15)
	Rivaroxaban	-	2.74 (0.42, 16.16)
	LMWH (standard dose; extended duration)	-	1.99 (0.21, 14.60)
	LMWH (low dose; pre-op)	-	3.13 (0.41, 23.59)
	VKA (extended duration)	-	8.21 (0.13, 7883.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.37 (0.00, 26.96)
	LMWH (high dose; extended duration)	-	2.06 (0.02, 2194.00)
Versus UFH	LMWH (high dose; standard duration)	0.60 (0.33, 1.06)	0.69 (0.28, 2.01)
	LMWH (standard dose; standard duration)	0.34 (0.14, 0.84)	0.71 (0.28, 2.13)
	Fondaparinux	-	1.18 (0.36, 5.06)
	LMWH (low dose; post-op)	-	0.61 (0.11, 3.68)
	VKA (standard duration)	-	0.43 (0.10, 2.01)
	Dabigatran	-	1.00 (0.25, 4.99)
	Apixaban	-	0.87 (0.16, 5.91)
	Rivaroxaban	-	0.76 (0.14, 4.22)
	LMWH (standard dose;	-	0.55 (0.07, 3.86)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	extended duration)		
	LMWH (low dose; pre-op)	-	0.87 (0.13, 6.53)
	VKA (extended duration)	-	2.29 (0.04, 2198.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.10 (0.00, 7.53)
	LMWH (high dose; extended duration)	-	0.57 (0.01, 621.20)
Versus LMWH (high dose; standard duration)	LMWH (standard dose; standard duration)	0.35 (0.09, 1.34)	1.04 (0.38, 2.83)
	Fondaparinux	1.83 (0.87, 3.85)*	1.71 (0.58, 5.66)
	LMWH (low dose; post-op)	-	0.89 (0.17, 4.54)
	VKA (standard duration)	0.68 (0.19, 2.40)	0.62 (0.16, 2.36)
	Dabigatran	-	1.46 (0.34, 6.58)
	Apixaban	-	1.27 (0.21, 7.77)
	Rivaroxaban	-	1.11 (0.19, 5.73)
	LMWH (standard dose; extended duration)	-	0.80 (0.09, 5.27)
	LMWH (low dose; pre-op)	-	1.26 (0.20, 8.08)
	VKA (extended duration)	-	3.28 (0.06, 2993.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.15 (0.00, 10.57)
	LMWH (high dose; extended duration)	-	0.83 (0.01, 851.90)
Versus LMWH (standard dose; standard duration)	Fondaparinux	1.48 (0.94, 2.34)*	1.66 (0.58, 5.15)
	LMWH (low dose; post-op)	0.51 (0.05, 5.66)	0.86 (0.18, 3.95)
	VKA (standard duration)	0.64 (0.18, 2.30)*	0.60 (0.16, 2.14)
	Dabigatran	1.38 (0.84, 2.28)*	1.41 (0.48, 4.27)
	Apixaban	1.22 (0.65, 2.26)*	1.23 (0.27, 5.51)
	Rivaroxaban	1.22 (0.65, 2.28)*	1.07 (0.25, 3.97)
	LMWH (standard dose; extended duration)	0.33 (0.01, 8.25)	0.78 (0.11, 3.85)
	LMWH (low dose; pre-op)	-	1.22 (0.20, 7.15)
	VKA (extended duration)	-	3.14 (0.06, 2820.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.14 (0.00, 8.94)
	LMWH (high dose; extended duration)	-	0.79 (0.01, 815.60)
Versus Fondaparinux	LMWH (low dose; post-op)	-	0.51 (0.08, 2.97)
	VKA (standard duration)	-	0.36 (0.07, 1.67)
	Dabigatran	-	0.85 (0.18, 3.89)
	Apixaban	-	0.74 (0.11, 4.58)
	Rivaroxaban	-	0.64 (0.10, 3.42)
	LMWH (standard dose;	-	0.47 (0.05, 3.11)

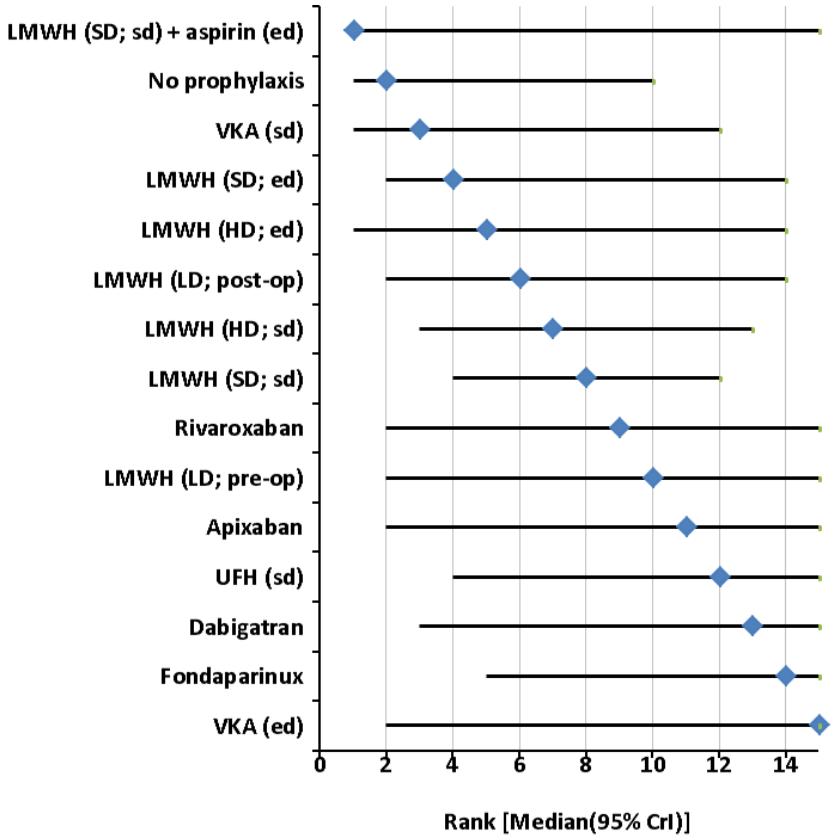
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	extended duration)		
	LMWH (low dose; pre-op)	-	0.73 (0.09, 5.23)
	VKA (extended duration)	-	1.90 (0.03, 1816.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.09 (0.00, 6.02)
	LMWH (high dose; extended duration)	-	0.48 (0.01, 500.80)
Versus LMWH (low dose; post-op)	VKA (standard duration)	-	0.70 (0.20, 2.61)
	Dabigatran	-	1.66 (0.26, 11.40)
	Apixaban	-	1.43 (0.17, 12.73)
	Rivaroxaban	-	1.25 (0.15, 9.64)
	LMWH (standard dose; extended duration)	-	0.90 (0.08, 8.49)
	LMWH (low dose; pre-op)	1.38 (0.86, 2.22)	1.42 (0.35, 5.91)
	VKA (extended duration)	-	3.68 (0.07, 3220.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.17 (0.00, 14.06)
	LMWH (high dose; extended duration)	-	0.93 (0.01, 927.10)
Versus VKA (standard duration)	Dabigatran	-	2.36 (0.45, 12.91)
	Apixaban	-	2.05 (0.29, 14.69)
	Rivaroxaban	-	1.77 (0.26, 11.11)
	LMWH (standard dose; extended duration)	-	1.29 (0.13, 10.07)
	LMWH (low dose; pre-op)	2.07 (1.22, 3.50)	2.03 (0.49, 8.27)
	VKA (extended duration)	2.89 (0.12, 71.31)	5.18 (0.12, 4147.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.24 (0.00, 18.31)
	LMWH (high dose; extended duration)	0.26 (0.13, 0.52)	1.30 (0.02, 1200.00)
Versus Dabigatran	Apixaban	-	0.87 (0.13, 5.46)
	Rivaroxaban	-	0.76 (0.12, 4.06)
	LMWH (standard dose; extended duration)	-	0.55 (0.06, 3.69)
	LMWH (low dose; pre-op)	-	0.86 (0.10, 6.78)
	VKA (extended duration)	-	2.26 (0.04, 2161.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.10 (0.00, 7.14)
	LMWH (high dose; extended duration)		0.57 (0.01, 607.50)
Versus Apixaban	Rivaroxaban	-	0.88 (0.10, 6.31)
	LMWH (standard dose;	-	0.63 (0.05, 5.52)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	extended duration)		
	LMWH (low dose; pre-op)	-	0.99 (0.10, 9.99)
	VKA (extended duration)	-	2.64 (0.04, 2645.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.12 (0.00, 9.43)
	LMWH (high dose; extended duration)	-	0.66 (0.01, 737.70)
Versus Rivaroxaban	LMWH (standard dose; extended duration)	0.82 (0.51, 1.30)	0.73 (0.18, 2.54)
	LMWH (low dose; pre-op)	-	1.14 (0.12, 11.40)
	VKA (extended duration)	-	3.01 (0.05, 3189.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.14 (0.00, 7.28)
	LMWH (high dose; extended duration)	-	0.76 (0.01, 905.60)
Versus LMWH (standard dose; extended duration)	LMWH (low dose; pre-op)	-	1.58 (0.15, 21.45)
	VKA (extended duration)	-	4.24 (0.06, 4892.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	0.35 (0.01, 8.51)*	0.20 (0.00, 8.19)
	LMWH (high dose; extended duration)	-	1.06 (0.01, 1347.00)
Versus LMWH (low dose; standard duration; pre-op)	VKA (extended duration)	-	2.62 (0.05, 2269.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.12 (0.00, 10.62)
	LMWH (high dose; extended duration)	-	0.66 (0.01, 652.50)
Versus VKA (extended duration	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.04 (0.00, 15.62)
	LMWH (high dose; extended duration)	-	0.25 (0.05, 1.14)
Versus LMWH (standard dose; standard duration) + aspirin (extended duration)	LMWH (high dose; extended duration)	-	6.97 (0.01, 64290.00)

**Intervention and comparison numbers have been switched in Review Manager*

Figure 832 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 14 different interventions being evaluated.

Figure 832: Rank order for interventions based the relative risk of experiencing major bleeding



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 275 compared with 276 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 55 reported. This corresponds well to the total number of trial arms, 51. The between trial standard deviation in the random effects analysis was 0.56 (95% CI 0.19 to 1.27). On evaluating inconsistency by comparing odd ratios, one inconsistency was identified. The NMA estimated odd ratio for LMWH at a standard dose for an extended duration versus VKA at a standard duration (1.30 [0.02, 1200.00]) lay outside of the confidence interval of the odd ratio estimated for the direct comparison (0.26 [0.13, 0.52]). An inconsistency model was run and the DIC statistics were as follows in Table 246. The difference in the DIC is small (<3-5) which suggests that there is no obvious inconsistency in the network. The consistency model has a smaller DIC suggesting that it is a better fit to the data than the inconsistency model.

Table 246: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – major bleeding

	DIC	ResDev
Consistency model	275.34	55
Inconsistency model	277.695	55

M.1.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 26 and Appendix H, deciding upon the most clinical and cost effective prophylaxis intervention in patients undergoing elective hip replacement surgery is challenging. In

order to overcome the difficulty of interpreting the conclusions from numerous separate comparisons, network meta-analysis of the direct evidence was performed. The findings of the NMA were used to facilitate the guideline committee in decision-making when developing recommendations.

Our analyses were divided into three critical outcomes. 42 studies informed the DVT network where 26 different individual or combination treatments were evaluated including five mechanical interventions, fourteen pharmacological interventions, and six interventions that combined both mechanical and pharmacological prophylaxis. 30 studies informed the PE network of 23 different treatments, including four mechanical interventions, eleven pharmacological interventions, and six interventions that combined both mechanical and pharmacological prophylaxis. The major bleeding network included 24 studies evaluating 15 treatments, 14 of which were pharmacological as for this outcome any mechanical prophylaxis measures were combined with the no prophylaxis intervention as it is believed that mechanical prophylaxis has no associated bleeding risk.

In the DVT network, the top three interventions were rivaroxaban, fondaparinux plus AES and LMWH at a standard dose for an extended duration plus AES. The bottom three interventions were no prophylaxis, UFH at an extended duration and IPCD (length unspecified). Five of the six interventions that represented a combination of mechanical and pharmacological prophylaxis featured in the top ten best ranked treatments. The treatment believed to most represent standard practice, LMWH at a standard dose for a standard duration plus AES, ranked at 7. There was a lot of uncertainty about the estimates with the credible intervals for some of the interventions being very wide, some interventions' ranks spanning across from 1 to 26.

In the PE network, the top intervention was the combination treatment of LMWH at a standard dose for a standard duration followed by aspirin at an extended duration. The second and third ranked treatments were LMWH at a high dose for an extended duration and LMWH at a high dose for a standard duration plus AES. The bottom three interventions were aspirin at a standard duration, foot pump andno prophylaxis. The intervention LMWH at a standard dose for a standard duration with AES was ranked eleventh. There was also considerable uncertainty in the PE network with wide credible intervals for a majority of the interventions, particularly for LMWH (high dose, standard duration) plus AES and LMWH (low dose, standard duration) plus AES with credible intervals spanning from 1 to 20.; and for AES (above-knee) and apixaban with credible intervals spanning from 2 to 23.

In the major bleeding network the highest ranked intervention was the combination treatment of LMWH at a standard dose for a standard duration followed by aspirin at an extended duration. This was followed by no prophylaxis and VKA at a standard duration.. The bottom three interventions were VKA at an extended duration, fondaparinux and dabigatran. There was a lot of uncertainty within the major bleeding network with very wide credible intervals for all of the interventions. These very wide credible intervals account for the unusual rank of no prophylaxis as the second best intervention in terms of major bleeding.

In summary, the three outcomes chosen for analyses were considered to be among the most critical for assessing clinical effectiveness of different VTE prophylaxis strategies. All three networks seemed to fit well, as demonstrated by DIC and residual deviance statistics. However due to the sparse nature of the networks, and low event rates, the credible intervals around the ranking of treatments in all three networks were wide suggesting considerable uncertainty about these results.

M.1.5 Conclusion

This analysis allowed us to combine findings from many different comparisons presented in the review even when direct comparative data was lacking.

The guideline committee and orthopaedic subgroup noted the wide credible intervals particularly for the PE and major bleeding network meta-analyses. They both also noted that even with the high levels of uncertainty, interventions such as LMWH at a standard dose for a standard duration followed by aspirin for an extended duration and LMWH in combination with AES, present possible clinical effectiveness in terms of the outcomes of DVT (symptomatic and asymptomatic), PE and major bleeding. .

For details of the rationale and discussion leading to recommendations, please refer to the section linking the evidence to the recommendations (section 26.6, chapter 26).

M.1.6 WinBUGS codes

M.1.6.1 WinBUGS code for number of patients with DVT (symptomatic and asymptomatic)

```
#Random effects model for multi-arm trials (any number of arms)

model{

for(i in 1:NS){

  w[i,1] <-0

  delta[i,t[i,1]]<-0

  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines

  for (k in 1:na[i]){

    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood

    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model

#Deviance residuals for data i

  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

   }

  sdev[i]<- sum(dev[i,1:na[i]])

  for (k in 2:na[i]){

# trial-specific LOR distributions

    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions

    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions

#adjustment, multi-arm RCTs

    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])

# cumulative adjustment for multi-arm trials

    sw[i,k] <-sum(w[i,1:k-1])/(k-1)
```

```
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[4] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 85642
a <- 4746
for (k in 1:3){       # treatments below 4
  logit(v[k]) <- logit(v[4]) - lor[k,4]      # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

for (k in 5:NT){    # treatments above 4
  logit(v[k]) <- logit(v[4]) + lor[4,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }
rr[4] <- v[4]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
```

```
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lor[c,k] <- d[k] - d[c]
    log(or[c,k]) <- lor[c,k]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}

# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.


list(NT=26, NS=42,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: general physical health indicators
m.tau= -1.26, sd.tau=1.25 )

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
13      14      12      32      8       32      NA      NA      NA      NA      1       2       4
        NA      NA      3
43      116     21      117     NA      NA      NA      NA      NA      NA      1       2       NA
        NA      NA      2
19      54      9       58      NA      NA      NA      NA      NA      NA      1       2       NA
        NA      NA      2
```

28	52 NA	22 NA	48 2	NA	NA	NA	NA	NA	NA	1	3	NA
36	75 NA	14 NA	68 2	NA	NA	NA	NA	NA	NA	1	3	NA
20	39 NA	4 NA	37 2	NA	NA	NA	NA	NA	NA	1	5	NA
36	152 NA	77 NA	158 2	NA	NA	NA	NA	NA	NA	1	6	NA
25	47 NA	15 NA	43 2	NA	NA	NA	NA	NA	NA	1	6	NA
28	136 NA	21 NA	142 3	8	136	NA	NA	NA	NA	2	3	5
1	79 NA	4 NA	79 2	NA	NA	NA	NA	NA	NA	2	3	NA
19	63 NA	25 NA	59 2	NA	NA	NA	NA	NA	NA	2	3	NA
15	120 NA	27 NA	106 2	NA	NA	NA	NA	NA	NA	2	3	NA
12	150 NA	5 NA	78 2	NA	NA	NA	NA	NA	NA	2	5	NA
8	190 NA	8 NA	196 2	NA	NA	NA	NA	NA	NA	2	6	NA
39	138 NA	15 NA	152 2	NA	NA	NA	NA	NA	NA	2	7	NA
12	102 NA	5 NA	113 2	NA	NA	NA	NA	NA	NA	2	7	NA
17	88 NA	6 NA	85 2	NA	NA	NA	NA	NA	NA	2	7	NA
67	783 NA	60 NA	791 2	NA	NA	NA	NA	NA	NA	2	8	NA
57	897 NA	45 NA	880 2	NA	NA	NA	NA	NA	NA	2	8	NA
18	138 NA	24 NA	136 2	NA	NA	NA	NA	NA	NA	2	9	NA
68	1911 NA	22 NA	1944 2	NA	NA	NA	NA	NA	NA	2	10	NA
71	869 NA	14 NA	864 2	NA	NA	NA	NA	NA	NA	2	11	NA
49	190 NA	28 NA	192 2	NA	NA	NA	NA	NA	NA	2	12	NA

24	116 NA	9 NA	101 2	NA	NA	NA	NA	NA	NA	3	5	NA
61	263 NA	50 NA	258 2	NA	NA	NA	NA	NA	NA	3	5	NA
4	33 NA	6 NA	28 2	NA	NA	NA	NA	NA	NA	3	13	NA
10	25 NA	7 NA	19 2	NA	NA	NA	NA	NA	NA	3	14	NA
27	80 NA	21 NA	81 3	36	86	NA	NA	NA	NA	4	15	18
33	104 NA	22 NA	114 2	NA	NA	NA	NA	NA	NA	4	16	NA
83	918 NA	36 NA	908 2	NA	NA	NA	NA	NA	NA	4	17	NA
11	78 NA	28 NA	75 2	NA	NA	NA	NA	NA	NA	4	18	NA
22	78 NA	33 NA	78 2	NA	NA	NA	NA	NA	NA	4	18	NA
11	66 NA	12 NA	72 2	NA	NA	NA	NA	NA	NA	6	12	NA
53	1558 NA	12 NA	1595 2	NA	NA	NA	NA	NA	NA	7	11	NA
81	338 NA	36 NA	337 3	44	336	NA	NA	NA	NA	12	19	20
8	176 NA	3 NA	184 2	NA	NA	NA	NA	NA	NA	12	21	NA
29	93 NA	44 NA	97 2	NA	NA	NA	NA	NA	NA	15	22	NA
44	784 NA	65 NA	796 2	NA	NA	NA	NA	NA	NA	17	23	NA
19	28 NA	8 NA	32 2	NA	NA	NA	NA	NA	NA	18	24	NA
4	39 NA	16 NA	40 2	NA	NA	NA	NA	NA	NA	18	25	NA
20	636 NA	15 NA	643 2	NA	NA	NA	NA	NA	NA	21	26	NA
23	65 NA	9 NA	67 2	NA	NA	NA	NA	NA	NA	24	25	NA

END

INITS

list(

d=c(NA,0,0,0,0, 0,0,0,1,2, 3,4,2,4,2, 1,2,-1,-2,0, 2,3,1,4,0, -1), # one for each treatment,

sd.sq=1,

mu=c(-2,0,2,0,0, 0,3,0,1,0, 0,2,1,1, 3, 2,-2,0,2,0, 0,0,3,0,1, 0,0,2,1, 1, 3, 2,1,0,4, 1, 2,0,2,-3, 1,1))

list(

d=c(NA,0,0,4,0, 0,3,0,0,3, 4,4,1,0,-1, -3,0,2,1,4, 2,1,2,2,1, 0), # one for each treatment,

sd.sq=0.1,

mu=c(0,0,-2,0,3, 0,0,2,0,0, 0,2,0,2,1, 4,0,0,-2,0, 3,0,0,2,0, 0,0,2,0,2, 1,4, 2,0, -3, 1,2,1,0,0, 1,1))

list(

d=c(NA,0,1,1,0, 0,0,0,1,2, 3,4,2,1,0, 3,1,3,4,-2, 0,1,-3,4,2, 1), # one for each treatment,

sd.sq=2,

mu=c(0,0,3,0,0, 0,0,0,3,3, 0,0,4,2,1, 1,0,0,3,0, 0,0,0,0,3, 3,0,0,4,2, 1,1,1, 2,4, 0,-1,2,1,3, 2,1))

M.1.6.2 WinBUGS code for inconsistency model for number of patients with DVT

VTE - inconsistency model - Elective hip DVT

==========

42 studies

26 treatments

==========

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){           # LOOP THROUGH STUDIES
  delta[i,1]<-0           # treatment effect is zero in control arm
  mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
  for (k in 1:na[i]) {    # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
```

```
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS

 Data
# DVT
# nt=no. treatments, ns=no. studies
list(nt=26,ns=42, m.tau= -1.26, sd.tau=1.25)

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
```

13	14 NA	12 NA	32 3	8	32	NA	NA	NA	NA	1	2	4
43	116 NA	21 NA	117 2	NA	NA	NA	NA	NA	NA	1	2	NA
19	54 NA	9 NA	58 2	NA	NA	NA	NA	NA	NA	1	2	NA
28	52 NA	22 NA	48 2	NA	NA	NA	NA	NA	NA	1	3	NA
36	75 NA	14 NA	68 2	NA	NA	NA	NA	NA	NA	1	3	NA
20	39 NA	4 NA	37 2	NA	NA	NA	NA	NA	NA	1	5	NA
36	152 NA	77 NA	158 2	NA	NA	NA	NA	NA	NA	1	6	NA
25	47 NA	15 NA	43 2	NA	NA	NA	NA	NA	NA	1	6	NA
28	136 NA	21 NA	142 3	8	136	NA	NA	NA	NA	2	3	5
1	79 NA	4 NA	79 2	NA	NA	NA	NA	NA	NA	2	3	NA
19	63 NA	25 NA	59 2	NA	NA	NA	NA	NA	NA	2	3	NA
15	120 NA	27 NA	106 2	NA	NA	NA	NA	NA	NA	2	3	NA
12	150 NA	5 NA	78 2	NA	NA	NA	NA	NA	NA	2	5	NA
8	190 NA	8 NA	196 2	NA	NA	NA	NA	NA	NA	2	6	NA
39	138 NA	15 NA	152 2	NA	NA	NA	NA	NA	NA	2	7	NA
12	102 NA	5 NA	113 2	NA	NA	NA	NA	NA	NA	2	7	NA
17	88 NA	6 NA	85 2	NA	NA	NA	NA	NA	NA	2	7	NA
67	783 NA	60 NA	791 2	NA	NA	NA	NA	NA	NA	2	8	NA
57	897 NA	45 NA	880 2	NA	NA	NA	NA	NA	NA	2	8	NA
18	138 NA	24 NA	136 2	NA	NA	NA	NA	NA	NA	2	9	NA

68	1911 NA	22 NA	1944 2	NA	NA	NA	NA	NA	NA	2	10	NA
71	869 NA	14 NA	864 2	NA	NA	NA	NA	NA	NA	2	11	NA
49	190 NA	28 NA	192 2	NA	NA	NA	NA	NA	NA	2	12	NA
24	116 NA	9 NA	101 2	NA	NA	NA	NA	NA	NA	3	5	NA
61	263 NA	50 NA	258 2	NA	NA	NA	NA	NA	NA	3	5	NA
4	33 NA	6 NA	28 2	NA	NA	NA	NA	NA	NA	3	13	NA
10	25 NA	7 NA	19 2	NA	NA	NA	NA	NA	NA	3	14	NA
27	80 NA	21 NA	81 3	36	86	NA	NA	NA	NA	4	15	18
33	104 NA	22 NA	114 2	NA	NA	NA	NA	NA	NA	4	16	NA
83	918 NA	36 NA	908 2	NA	NA	NA	NA	NA	NA	4	17	NA
11	78 NA	28 NA	75 2	NA	NA	NA	NA	NA	NA	4	18	NA
22	78 NA	33 NA	78 2	NA	NA	NA	NA	NA	NA	4	18	NA
11	66 NA	12 NA	72 2	NA	NA	NA	NA	NA	NA	6	12	NA
53	1558 NA	12 NA	1595 2	NA	NA	NA	NA	NA	NA	7	11	NA
81	338 NA	36 NA	337 3	44	336	NA	NA	NA	NA	12	19	20
8	176 NA	3 NA	184 2	NA	NA	NA	NA	NA	NA	12	21	NA
29	93 NA	44 NA	97 2	NA	NA	NA	NA	NA	NA	15	22	NA
44	784 NA	65 NA	796 2	NA	NA	NA	NA	NA	NA	17	23	NA
19	28 NA	8 NA	32 2	NA	NA	NA	NA	NA	NA	18	24	NA
4	39 NA	16 NA	40 2	NA	NA	NA	NA	NA	NA	18	25	NA

20	636	15	643	NA	NA	NA	NA	NA	NA	21	26	NA
	NA	NA	2									
23	65	9	67	NA	NA	NA	NA	NA	NA	24	25	NA
	NA	NA	2									

END

INITS

#chain 1

list(sd.sq=1, mu=c(-2,0,2,0,0, 0,3,0,1,0, 0,2,1,1, 3, 2,-2,0,2,0, 0,0,3,0,1, 0,0,2,1,1, 3, 2,1,0,4, 1, 2,0,2,0, 1,2),

d = structure(.Data = c(

NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

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NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,

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      NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,
     NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,
   NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,
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NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA, NA,0,0,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0  ),
.Dim = c(25,26))   )


# chain 2
list(sd.sq=1.5,  mu=c(0,0,-2,0,3,   0,0,2,0,0,  0,2,0,2,1,   4,0,0,-2,0,   3,0,0,2,0,   0,0,2,0,2,  1,4,2,0,-3,
1,2,1,0, 2,    2,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
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        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,
```

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NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA, NA,NA,5 ),

.Dim = c(25,26))  )



# chain 3

list(sd.sq=3,  mu=c(0,0,3,0,0,  0,0,0,3,3,  0,0,4,2,1,1,0,0,3,0,0,  0,0,0,3,3,  0,0,4,2,1,1, 1, 2,4, 0,-1,2,1,1,
0,-1),

d = structure(.Data = c(

NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-
3,-3,-3,-3,-3,
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NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,

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NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3
),

.Dim = c(25,26)))

M.1.6.3 WinBUGS code for number of patients with PE

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  sdev[i]<- sum(dev[i,1:na[i]])
  for (k in 2:na[i]){
# trial-specific LOR distributions
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
```

```
# cumulative adjustment for multi-arm trials
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[3] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 85642
a <- 583
for (k in 1:2){       # treatments below 3
  logit(v[k]) <- logit(v[3]) - lor[k,3]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

for (k in 4:NT){    # treatments above 3
  logit(v[k]) <- logit(v[3]) + lor[3,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

rr[3] <- v[3]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
```

```
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lor[c,k] <- d[k] - d[c]
    log(or[c,k]) <- lor[c,k]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}

# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 4.

list(NT=23, NS=30,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: general physical health indicators
m.tau= -1.26, sd.tau=1.25  )

  r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 5 14 3 32 2 32 NA NA NA NA 1 2 3 NA NA 3
 2.5 117 0.5 118 NA NA NA NA NA NA 1 2 NA NA NA 2
 1.5 55 0.5 59 NA NA NA NA NA NA 1 2 NA NA NA 2
 1 158 1 152 NA NA NA NA NA NA 1 4 NA NA NA 2
```

2 196 2 194 NA NA NA NA NA NA 2 4 NA NA NA 2

1.5 204 4.5 210 0.5 196 NA NA NA NA 2 5 8 NA NA 3

0.5 85 1.5 84 NA NA NA NA NA NA 2 5 NA NA NA 2

1 67 2 69 NA NA NA NA NA NA 2 5 NA NA NA 2

0.5 121 1.5 107 NA NA NA NA NA NA 2 5 NA NA NA 2

4 869 1 864 NA NA NA NA NA NA 2 6 NA NA NA 2

1.5 212 0.5 225 NA NA NA NA NA NA 2 7 NA NA NA 2

2 992 1 1001 NA NA NA NA NA NA 2 9 NA NA NA 2

3 897 5 880 NA NA NA NA NA NA 2 9 NA NA NA 2

0.5 139 1.5 137 NA NA NA NA NA NA 2 10 NA NA NA 2

5 2699 3 2708 NA NA NA NA NA NA 2 11 NA NA NA 2

1.5 81 0.5 87 0.5 82 NA NA NA NA 3 12 13 NA NA 3

1 78 2 78 NA NA NA NA NA NA 3 12 NA NA NA 2

3 1123 3 1129 NA NA NA NA NA NA 3 14 NA NA NA 2

3.5 107 0.5 112 NA NA NA NA NA NA 3 15 NA NA NA 2

2 134 1 125 NA NA NA NA NA NA 5 8 NA NA NA 2

1 332 1 333 NA NA NA NA NA NA 5 8 NA NA NA 2

0.5 26 1.5 20 NA NA NA NA NA NA 5 16 NA NA NA 2

4 1595 1 1558 NA NA NA NA NA NA 6 7 NA NA NA 2

3.5 399 0.5 381 NA NA NA NA NA NA 7 17 NA NA NA 2

6 1516 9 1495 NA NA NA NA NA NA 8 18 NA NA NA 2

1 32 3 35 NA NA NA NA NA NA 12 19 NA NA NA 2

0.5 94 1.5 98 NA NA NA NA NA NA 13 20 NA NA NA 2

5.5 1127 0.5 1129 NA NA NA NA NA NA 14 21 NA NA NA 2

1.5 177 0.5 185 NA NA NA NA NA NA 18 22 NA NA NA 2

4.5 637 0.5 644 NA NA NA NA NA NA 22 23 NA NA NA 2

END

list(

d=c(NA,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0, 0), # one for each treatment,

```
sd.sq=1,
mu=c(0,0,0,0,0,   0,0,0,0,0,   0,0,0,0,0,   0, 0,0,0,0,   0,0,0,0,0,    0,0,0,0,0) )

list(
d=c(NA,0,0,0,0,   0,0,0,0,1,  0,0,0,0,-1,   0,0,0,0,1,  0,-1, 0), # one for each treatment,
sd.sq=0.1,
mu=c(-1,-1,-1,-1,-1,   -1,-1,-1,-1,-1,   -1,-1,-1,-1,-1,   -1, -1,-1,-1,-1,   -1,-1,-1,-1,-1,   -1,-1,-1,-1,-1) )

list(
d=c(NA,0,0,0,2,   -2,0,0,0,1,  0,0,0,0,-1,   2,0,0,0,1,  -2,-1, -1), # one for each treatment,
sd.sq=2,
mu=c(0,1,-1,0,2,   0,1,-1,-2,0,   1,2,0,2,0,   0, 2,1,0,-2,  0,2,1,-2,0,  2,1,1,0,0) )
```

M.1.6.4 WinBUGS code for inconsistency model for number of patients with PE

```
VTE - inconsistency model - Elective hip PE
==============================
30 studies
23 treatments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){           # LOOP THROUGH STUDIES
   delta[i,1]<-0          # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
```

```
        + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS


 Data
# DVT
# nt=no. treatments, ns=no. studies
list(nt=23,ns=30, m.tau= -1.26, sd.tau=1.25)


  r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 5 14 3 32 2 32 NA NA NA NA 1 2 3 NA NA 3
 2.5 117 0.5 118 NA NA NA NA NA NA 1 2 NA NA NA 2
 1.5 55 0.5 59 NA NA NA NA NA NA 1 2 NA NA NA 2
```

1 158 1 152 NA NA NA NA NA NA 1 4 NA NA NA 2

2 196 2 194 NA NA NA NA NA NA 2 4 NA NA NA 2

1.5 204 4.5 210 0.5 196 NA NA NA NA 2 5 8 NA NA 3

0.5 85 1.5 84 NA NA NA NA NA NA 2 5 NA NA NA 2

1 67 2 69 NA NA NA NA NA NA 2 5 NA NA NA 2

0.5 121 1.5 107 NA NA NA NA NA NA 2 5 NA NA NA 2

4 869 1 864 NA NA NA NA NA NA 2 6 NA NA NA 2

1.5 212 0.5 225 NA NA NA NA NA NA 2 7 NA NA NA 2

2 992 1 1001 NA NA NA NA NA NA 2 9 NA NA NA 2

3 897 5 880 NA NA NA NA NA NA 2 9 NA NA NA 2

0.5 139 1.5 137 NA NA NA NA NA NA 2 10 NA NA NA 2

5 2699 3 2708 NA NA NA NA NA NA 2 11 NA NA NA 2

1.5 81 0.5 87 0.5 82 NA NA NA NA 3 12 13 NA NA 3

1 78 2 78 NA NA NA NA NA NA 3 12 NA NA NA 2

3 1123 3 1129 NA NA NA NA NA NA 3 14 NA NA NA 2

3.5 107 0.5 112 NA NA NA NA NA NA 3 15 NA NA NA 2

2 134 1 125 NA NA NA NA NA NA 5 8 NA NA NA 2

1 332 1 333 NA NA NA NA NA NA 5 8 NA NA NA 2

0.5 26 1.5 20 NA NA NA NA NA NA 5 16 NA NA NA 2

4 1595 1 1558 NA NA NA NA NA NA 6 7 NA NA NA 2

3.5 399 0.5 381 NA NA NA NA NA NA 7 17 NA NA NA 2

6 1516 9 1495 NA NA NA NA NA NA 8 18 NA NA NA 2

1 32 3 35 NA NA NA NA NA NA 12 19 NA NA NA 2

0.5 94 1.5 98 NA NA NA NA NA NA 13 20 NA NA NA 2

5.5 1127 0.5 1129 NA NA NA NA NA NA 14 21 NA NA NA 2

1.5 177 0.5 185 NA NA NA NA NA NA 18 22 NA NA NA 2

4.5 637 0.5 644 NA NA NA NA NA NA 22 23 NA NA NA 2

END

INITS

#chain 1

list(sd.sq=1, mu=c(0,0,3,0,0, 0,2,0,-1,0, 4,0,3,1,0, 0, 2,1,3,-2, 4,2,1,-3,0, 3,1,0,3,-2),

```
d = structure(.Data = c(
        NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,
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        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0
),
.Dim = c(22,23))   )

# chain 2
list(sd.sq=1.5,  mu=c(0,2,1,0,-2,   0,3,0,4,0,    2,0,1,3,0,    0, 2,1,3,-2,    4,2,1,-3,0,   3,2,-1,0,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
```

```
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
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        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,
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        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5
),
.Dim = c(22,23))  )

# chain 3
list(sd.sq=3,  mu=c(0,3,3,0,4,   0,1,0,-2,0,   1,2,0,2,0,   0, 2,1,3,-2,    4,2,1,-3,0,   3,1,1,0,-1),
d = structure(.Data = c(
        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
```

```
        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
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        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3
),
.Dim = c(22,23))  )
```

M.1.6.5 WinBUGS code for number of patients with major bleeding

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  sdev[i]<- sum(dev[i,1:na[i]])
```

```
  for (k in 2:na[i]){
# trial-specific LOR distributions
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <-sum(w[i,1:k-1])/(k-1)
   }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[4] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 85642
a <- 620
for (k in 1:3){       # treatments below 4
  logit(v[k]) <- logit(v[4]) - lor[k,4]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }
```

```
for (k in 5:NT){    # treatments above 4
  logit(v[k]) <- logit(v[4]) + lor[4,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

rr[4] <- v[4]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lor[c,k] <- d[k] - d[c]
    log(or[c,k]) <- lor[c,k]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}

# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.

list(NT=15, NS=24,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: adverse events
```

m.tau= -0.84, sd.tau=1.24)

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	r[,4]	n[,4]	r[,5]	n[,5]	t[,1]	t[,2]	t[,3]	t[,4]	t[,5]	na[]
3.5	36	0.5	33	NA	NA	NA	NA	NA	NA	1	2	NA	NA	NA	2
1	50	2	50	NA	NA	NA	NA	NA	NA	1	3	NA	NA	NA	2
0.5	102	2.5	103	1.5	101	NA	NA	NA	NA	1	4	6	NA	NA	3
0.5	199	11.5	195	NA	NA	NA	NA	NA	NA	1	4	NA	NA	NA	2
1	75	1	78	NA	NA	NA	NA	NA	NA	1	4	NA	NA	NA	2
0.5	83	2.5	82	NA	NA	NA	NA	NA	NA	1	5	NA	NA	NA	2
19	332	11	333	NA	NA	NA	NA	NA	NA	2	3	NA	NA	NA	2
13	209	8	195	3	203	NA	NA	NA	NA	2	3	4	NA	NA	3
5	69	1	67	NA	NA	NA	NA	NA	NA	2	4	NA	NA	NA	2
0.5	107	2.5	121	NA	NA	NA	NA	NA	NA	2	4	NA	NA	NA	2
11	1129	20	1128	NA	NA	NA	NA	NA	NA	3	5	NA	NA	NA	2
6	1516	4	1495	NA	NA	NA	NA	NA	NA	3	7	NA	NA	NA	2
32	1133	47	1140	NA	NA	NA	NA	NA	NA	4	5	NA	NA	NA	2
6	271	4	279	NA	NA	NA	NA	NA	NA	4	7	NA	NA	NA	2
9	1003	14	1010	NA	NA	NA	NA	NA	NA	4	8	NA	NA	NA	2
18	1154	23	1146	NA	NA	NA	NA	NA	NA	4	8	NA	NA	NA	2
18	2659	22	2673	NA	NA	NA	NA	NA	NA	4	9	NA	NA	NA	2

19	1257	23	1252	NA	NA	NA	NA	NA	NA	4	10	NA
	NA	NA	2									
1.5	142	0.5	141	NA	NA	NA	NA	NA	NA	4	11	NA
	NA	NA	2									
32	487	22	489	44	496	NA	NA	NA	NA	6	7	12
	NA	NA	3									
0.5	177	1.5	185	NA	NA	NA	NA	NA	NA	7	13	NA
	NA	NA	2									
40	2266	33	2275	NA	NA	NA	NA	NA	NA	10	11	NA
	NA	NA	2									
1.5	401	0.5	386	NA	NA	NA	NA	NA	NA	11	14	NA
	NA	NA	2									
37	636	10	643	NA	NA	NA	NA	NA	NA	13	15	NA
	NA	NA	2									

END

INITS

list(

d=c(NA,0,0,0,0, 0,0,0,1,2, 3,4,1,0,0), # one for each treatment

sd.sq=1,

mu=c(-2,0,2,0,0, 0,3,0,1,0, 0,2,1, 1, 3, 2,0, 0,1,2, 1,2,1,1))

list(

d=c(NA,0,0,4,0, 0,3,0,0,3, 4,4,2,1,2), # one for each treatment

sd.sq=0.1,

mu=c(0,0,-2,0,3, 0,0,2,0,0, 0,2,0,2,1, 4,3,0,3,4, 1,0,-1,0))

list(

d=c(NA,0,1,1,0, 0,0,0,1,2, 3,4,1,2,1), # one for each treatment

sd.sq=2,

mu=c(0,0,3,0,0, 0,0,0,3,3, 0,0,4,2,1, 1,-1,0,2,3, 2,-3,0,2))

M.1.6.6 WinBUGS code for inconsistency model for number of patients with major bleeding

VTE - inconsistency model - Elective hip - major bleeding

```
==============================
24 studies
15 treatments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){           # LOOP THROUGH STUDIES
   delta[i,1]<-0          # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
     }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
```

```
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var

prec.tau <- pow(sd.tau,-2)

tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)

sd <- sqrt(sd.sq)


} # *** PROGRAM ENDS


 Data

# DVT

# nt=no. treatments, ns=no. studies

list(nt=15,ns=24, m.tau= -0.84, sd.tau=1.24)


 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]

3.5     36      0.5     33      NA      NA      NA      NA      NA      NA      1       2       NA
        NA      NA      2

1       50      2       50      NA      NA      NA      NA      NA      NA      1       3       NA
        NA      NA      2

0.5     102     2.5     103     1.5     101     NA      NA      NA      NA      1       4       6
        NA      NA      3

0.5     199     11.5    195     NA      NA      NA      NA      NA      NA      1       4       NA
        NA      NA      2

1       75      1       78      NA      NA      NA      NA      NA      NA      1       4       NA
        NA      NA      2

0.5     83      2.5     82      NA      NA      NA      NA      NA      NA      1       5       NA
        NA      NA      2

19      332     11      333     NA      NA      NA      NA      NA      NA      2       3       NA
        NA      NA      2

13      209     8       195     3       203     NA      NA      NA      NA      2       3       4
        NA      NA      3

5       69      1       67      NA      NA      NA      NA      NA      NA      2       4       NA
        NA      NA      2

0.5     107     2.5     121     NA      NA      NA      NA      NA      NA      2       4       NA
        NA      NA      2

11      1129    20      1128    NA      NA      NA      NA      NA      NA      3       5       NA
        NA      NA      2

6       1516    4       1495    NA      NA      NA      NA      NA      NA      3       7       NA
        NA      NA      2
```

32	1133 NA	47 NA	1140 2	NA	NA	NA	NA	NA	NA	4	5	NA
6	271 NA	4 NA	279 2	NA	NA	NA	NA	NA	NA	4	7	NA
9	1003 NA	14 NA	1010 2	NA	NA	NA	NA	NA	NA	4	8	NA
18	1154 NA	23 NA	1146 2	NA	NA	NA	NA	NA	NA	4	8	NA
18	2659 NA	22 NA	2673 2	NA	NA	NA	NA	NA	NA	4	9	NA
19	1257 NA	23 NA	1252 2	NA	NA	NA	NA	NA	NA	4	10	NA
1.5	142 NA	0.5 NA	141 2	NA	NA	NA	NA	NA	NA	4	11	NA
32	487 NA	22 NA	489 3	44	496	NA	NA	NA	NA	6	7	12
0.5	177 NA	1.5 NA	185 2	NA	NA	NA	NA	NA	NA	7	13	NA
40	2266 NA	33 NA	2275 2	NA	NA	NA	NA	NA	NA	10	11	NA
1.5	401 NA	0.5 NA	386 2	NA	NA	NA	NA	NA	NA	11	14	NA
37	636 NA	10 NA	643 2	NA	NA	NA	NA	NA	NA	13	15	NA

END

INITS

#chain 1

list(sd.sq=1, mu=c(-2,0,2,0,0, 0,3,0,1,0, 0,2,1,1,3, 2,-2,1,1,0, 0,0,0,0),

d = structure(.Data = c(

NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,

```
        NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0),
.Dim = c(14,15))   )

# chain 2
list(sd.sq=1.5,  mu=c(0,0,-2,0,3,  0,0,2,0,0,   0,2,0,2,1,  4,0,2,-1,1,    0,1,0,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5 ),
.Dim = c(14,15))  )

# chain 3
list(sd.sq=3,  mu=c(0,0,3,0,0,  0,0,0,3,3,  0,0,4,2,1,  1,0,3,0,0,     2,1,0,0),
d = structure(.Data = c(
```

```
        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3),
.Dim = c(14,15))  )
```

M.2 Network meta-analysis for elective knee replacement surgery

M.2.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles for Chapter 27 and forest plots in Appendix L) does not help inform which intervention is most effective as VTE prophylaxis in patients undergoing elective knee replacement surgery. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different treatments; in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial.
- There are frequently multiple overlapping comparisons that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions. In this case the outcomes were defined as:

- Deep vein thrombosis (DVT; symptomatic and asymptomatic)
- Pulmonary embolism (PE)
- Major bleeding

The analysis also provided 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.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term "network" better describes the data structure, whereas "mixed treatments" could easily be misinterpreted as referring to combinations of treatments.

M.2.2 Methods

M.2.2.1 Study selection

To estimate the relative risks, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

M.2.2.2 Outcome measures

The NMA evidence reviews for interventions considered three clinical efficacy outcomes identified from the clinical evidence review; number of people with DVT, number of people with PE and number of people with major bleeding. Other outcomes were not considered for the NMA as they were infrequently reported across the studies. The guideline committee considered that these outcomes were the most critical clinical outcomes for testing effectiveness of VTE prophylaxis.

M.2.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical evidence review already presented in Chapter 27 of the full guideline and in Appendix H. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in each network are shown in Table 247.

Table 247: Treatments included in the network meta-analysis

Network 1: Number of people with DVT	Network 2: Number of people with PE	Network 3: Number of people with major bleeding
No prophylaxis	No prophylaxis	No prophylaxis/mechanical
LMWH (standard dose; standard duration)	LMWH (standard dose; standard duration)	LMWH (standard dose; standard duration)
LMWH (high dose; standard duration)	AES	LMWH (high dose; standard duration)
AES (length unspecified)	IPCD	Fondaparinux
Dabigatran	Dabigatran	LMWH (low dose; standard duration)
IPCD (length unspecified)	Rivaroxaban	Apixaban
Foot pump	Apixaban	Dabigatran
Foot pump + AES	LMWH (standard dose; extended duration)	Rivaroxaban
Rivaroxaban	LMWH (standard dose; standard duration) + AES	LMWH (standard dose; extended duration)
Aspirin	LMWH (low dose; standard duration) + AES	UFH
LMWH (standard duration; extended duration)	LMWH (high dose; standard duration)	VKA
Apixaban	VKA	-
VKA	UFH	-
UFH	-	-
Fondaparinux + AES	-	-
LMWH (standard dose; standard duration) + AES	-	-
LMWH (low dose; standard duration) + AES	-	-
LMWH high dose; standard duration) + AES	-	-
UFH + AES	-	-

M.2.2.4 Baseline risks

The baseline risk is defined as the risk of achieving the outcome of interest in the baseline treatment arm of the included trials. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks. However, the majority of these trials were older studies that reported very high risk of DVT and PE in the no prophylaxis arm that the orthopaedic subgroup considered to be not reflective of the baseline risk in the UK. Hence, for the purpose of calculating the relative risks of these events for presentation in this appendix, the baseline risk values were obtained from data from the UK National Joint Registry (NJR).[450] For full details of the calculation of baseline risk, please refer to HE write-up (Appendix P, section P.1.3.3).

M.2.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a three-arm random effects model template for the networks, from the University of

Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome subgroup, a diagram of the evidence network is presented in section M.2.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. Due to the sparse nature of the networks (few studies per direct treatment comparison), the between-study heterogeneity parameter is imprecisely estimated in a random effects model. Therefore it is beneficial to apply informative priors in order to restrict the prior distribution for heterogeneity to avoid unreasonably wide credible intervals. Turner et al (2015)[946] derived a novel set of predictive distributions for the degree of heterogeneity across 80 different settings. Appropriate predictive distributions for heterogeneity were chosen from Turner et al (2015)[946] and used directly as informative priors. The log normal (μ, σ^2) predictive distributions obtained for the between-study heterogeneity in a future meta-analysis presented in Table IV[946] were selected according to the outcome and treatment comparison. For the DVT and PE NMAs the distributions defined by the outcome of "general physical health indicators" and by the intervention/comparison type "non-pharmacological vs. pharmacological" were chosen (LN[-1.26, 1.25^2]). For the major bleeding NMA the distributions defined by the outcome of "adverse events" and by the intervention/comparison type "non-pharmacological vs. pharmacological" were chosen (LN[-0.84, 1.24^2]). These distributions were chosen as they represented outcomes measured by an assessor, whose method of measurement as well as judgement may influence the outcome (as studies provided slightly variable ways of defining these critical outcomes), and the interaction aspect encompassed both the pharmacological and mechanical prophylaxis options covered in our review protocol.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 27, and Appendix H).

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and treatment specific absolute probability respectively. Then:

$$\tilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$\boldsymbol{p} = \frac{\boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}{\mathbf{1} + \boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability ($\boldsymbol{p_b}$) to get treatment specific relative risks ($\boldsymbol{rr_b}$):

$$p_b = \frac{e^{BO}}{1 + e^{BO}}$$

$$rr_b = \frac{p}{p_b}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

We also calculated the overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the relative risks from the direct evidence (from pair-wise meta-analysis) to the relative risks from the combined direct and indirect evidence (from NMA). We further tested for inconsistency by developing inconsistency models for networks of binary outcomes using the TSD 4 template from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). We compared the posterior mean of the residual deviance between the consistency and inconsistency models to see which was a better fit to the data (closest to the number of trial arms in each network) and checked the difference in deviance information criterion (DIC) values between the two models was small (less than 3-5) or if it was larger, that the smaller DIC and hence better fitting model was the consistency model. No inconsistency was identified.

M.2.3 Results

M.2.3.1 Deep vein thrombosis (symptomatic and asymptomatic)

Included studies

26 studies were identified as reporting on DVT (symptomatic and asymptomatic) outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 23 studies involving 19 treatments were included in the network for DVT. The network can be seen in **Figure 833** and the trial data for each of the studies included in the NMA are presented in **Table 248**.

Figure 833: Network diagram for DVT

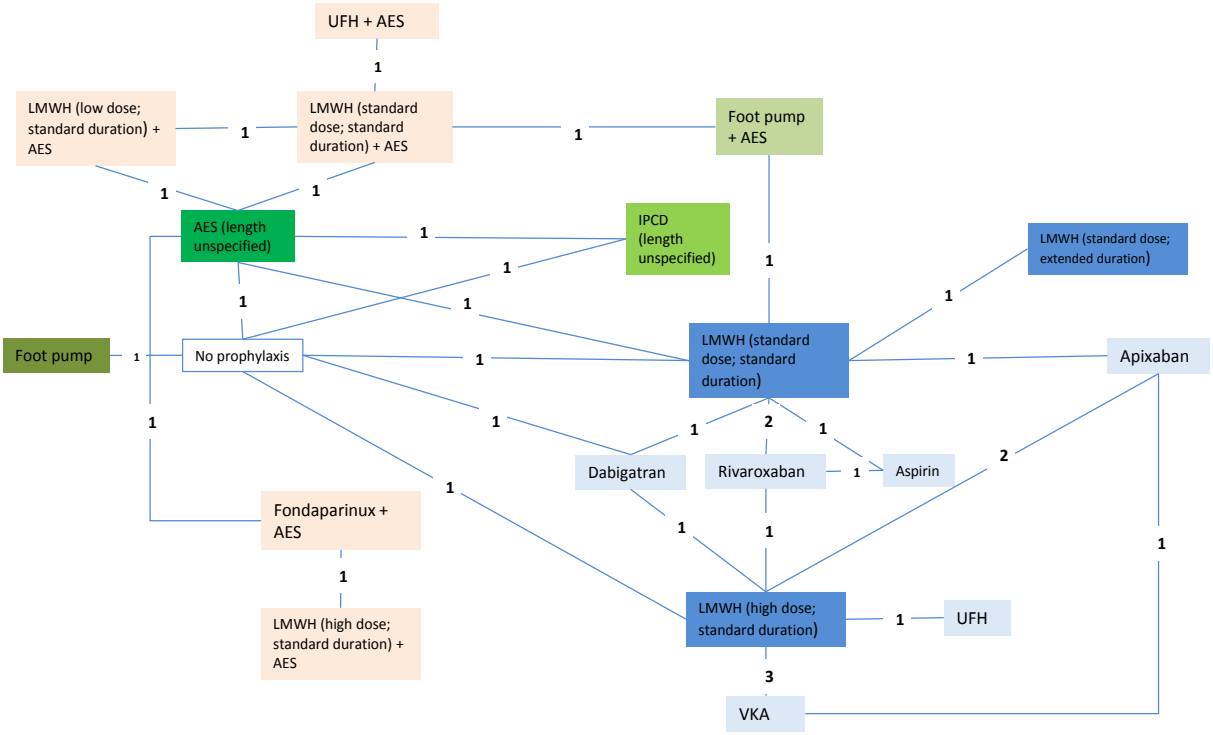


Table 248: Study data for DVT network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Intervention 3	Comparison		Intervention 1		Intervention 2		Intervention 3	
					N	NA	N	NA	N	NA		
Chin 2009 [177]	No prophylaxis	LMWH (standard dose; standard duration)	AES (length unspecified)	IPCD (length unspecified)	24	110	6	110	14	110	9	110
Leclerc 1992 [543]	No prophylaxis	LMWH (high dose; standard duration)	-	-	37	64	11	65	-	-	-	-
Wilson 1992 [1014]	No prophylaxis	Foot pump	-	-	19	32	5	28	-	-	-	-
Fuji 2010[320]	No prophylaxis	Dabigatran	-	-	57	101	23	96	-	-	-	-
Blanchard 1999A [106]	LMWH (standard dose; standard duration)	IPCD (length unspecified)	-	-	16	67	34	63	-	-	-	-
Norgren 1998 [700]	LMWH (standard dose; standard duration)	Foot pump + AES	-	-	0	14	4	15	-	-	-	-
Zou 2014 [1052]	LMWH (standard dose; standard duration)	Rivaroxaban	Aspirin	-	14	112	3	102	18	110	-	-
Lassen 2008 [525]	LMWH (standard dose; standard	Rivaroxaban	-	-	160	878	79	824	-	-	-	-

Study	Comparison	Intervention 1	Intervention 2	Intervention 3	Comparison		Intervention 1		Intervention 2		Intervention 3	
	duration)											
Eriksson 2007 [293]	LMWH (standard dose; standard duration)	Dabigatran	-	-	192	685	182	675	-	-	-	-
Comp 2001 [208]	LMWH (standard dose; standard duration)	LMWH (standard duration; extended duration)	-	-	37	144	33	155	-	-	-	-
Lassen 2010 [535]	LMWH (standard dose; standard duration)	Apixaban	-	-	243	997	142	971	-	-	-	-
Turpie 2009 [956]	LMWH (high dose; standard duration)	Rivaroxaban	-	-	86	959	61	965	-	-	-	-
Ginsberg 2009 [792]	LMWH (high dose; standard duration)	Dabigatran	-	-	158	643	181	604	-	-	-	-
Lassen 2007[532]	LMWH (high dose; standard duration)	Apixaban	VKA	-	15	109	21	208	29	109	-	-
Lassen 2009 [536]	LMWH (high dose; standard duration)	Apixaban	-	-	92	1122	89	1142	-	-	-	-
Fitzgerald	LMWH (high	VKA	-	-	44	173	79	176	-	-	-	-

Study	Comparison	Intervention 1	Intervention 2	Intervention 3	Comparison		Intervention 1		Intervention 2		Intervention 3	
2001 [308]	dose; standard duration)											
Leclerc 1996 [544]	LMWH (high dose; standard duration)	VKA	-	-	76	206	109	211	-	-	-	-
Colwell 1995D [205]	LMWH (high dose; standard duration)	UFH	-	-	56	145	77	143	-	-	-	-
Cho 2013 [178]	AES (length unspecified)	Fondaparinux + AES	-	-	19	74	5	74	-	-	-	-
Fuji 2008A [328]	AES (length unspecified)	LMWH (standard dose; standard duration) + AES	LMWH low dose; standard duration) + AES	-	48	79	34	78	26	74	-	-
Warwick 2002 [995]	Foot pump + AES	LMWH (standard dose; standard duration) + AES	-	-	57	99	48	89	-	-	-	-
Bauer 2001 [78]	Fondaparinux + AES	LMWH (high dose; standard duration) + AES	-	-	45	361	98	361	-	-	-	-
Fauno 1994 [301]	LMWH (standard dose; standard duration) + AES	UFH + AES	-	-	21	91	25	93	-	-	-	-

N; number of events, NA; number analysed

NMA results - DVT

Table 249summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 249: Risk ratios for DVT (symptomatic and asymptomatic)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	LMWH (standard dose; standard duration)	0.25 (0.11, 0.59)	0.26 (0.15, 0.43)
	LMWH (high dose; standard duration)	0.29 (0.16, 0.52)	0.18 (0.10, 0.30)
	AES (length unspecified)	0.58 (0.32, 1.07)	0.88 (0.55, 1.56)
	Dabigatran	0.42 (0.29, 0.63)	0.25 (0.14, 0.42)
	IPCD (length unspecified)	0.38 (0.18, 0.77)	0.61 (0.32, 1.04)
	Foot pump	0.30 (0.13, 0.70)	0.20 (0.05, 0.63)
	Foot pump + AES	-	0.55 (0.25, 1.48)
	Rivaroxaban	-	0.12 (0.06, 0.22)
	Aspirin	-	0.41 (0.16, 0.94)
	LMWH (standard dose; extended duration)	-	0.21 (0.08, 0.49)
	Apixaban	-	0.15 (0.07, 0.26)
	VKA	-	0.35 (0.17, 0.65)
	UFH	-	0.31 (0.13, 0.69)
	Fondaparinux + AES	-	0.35 (0.16, 0.67)
	LMWH (standard dose; standard duration) + AES	-	0.42 (0.24, 1.00)
	LMWH (low dose; standard duration) + AES	-	0.56 (0.26, 1.32)
	LMWH high dose; standard duration) + AES	-	0.77 (0.31, 1.57)
	UFH + AES	-	0.50 (0.19, 1.50)
Versus LMWH (standard dose; standard duration)	LMWH (high dose; standard duration)	-	0.69 (0.44, 1.05)
	AES (length unspecified)	2.33 (0.93, 5.85)*	3.45 (1.83, 7.10)
	Dabigatran	1.29 (1.09, 1.53)*	0.97 (0.64, 1.52)
	IPCD (length unspecified)	2.05 (1.32, 3.17)*	2.33 (1.31, 4.19)
	Foot pump	-	0.77 (0.18, 2.70)
	Foot pump + AES	8.44 (0.50, 143.77)*	2.15 (0.81, 6.66)
	Rivaroxaban	0.50 (0.39, 0.64)*	0.46 (0.28, 0.70)
	Aspirin	1.31 (0.69, 2.50)*	1.59 (0.71, 3.32)
	LMWH (standard dose; extended duration)	0.83 (0.55, 1.25)	0.80 (0.38, 1.63)
	Apixaban	0.60 (0.50, 0.72)*	0.57 (0.35, 0.88)
	VKA	-	1.33 (0.71, 2.43)
	UFH	-	1.21 (0.54, 2.59)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	Fondaparinux + AES	-	1.35 (0.68, 2.59)
	LMWH (standard dose; standard duration) + AES	-	1.67 (0.70, 4.69)
	LMWH (low dose; standard duration) + AES	-	2.17 (0.87, 5.97)
	LMWH high dose; standard duration) + AES	-	2.94 (1.25, 6.49)
	UFH + AES	-	1.97 (0.62, 6.92)
Versus LMWH (high dose; standard duration)	AES (length unspecified)	-	5.04 (2.52, 10.94)
	Dabigatran	1.22 (1.02, 1.46)*	1.41 (0.93, 2.26)
	IPCD (length unspecified)	-	3.40 (1.74, 6.70)
	Foot pump	-	1.13 (0.26, 3.98)
	Foot pump + AES	-	3.13 (1.10, 10.34)
	Rivaroxaban	0.70 (0.51, 0.97)*	0.67 (0.39, 1.06)
	Aspirin	-	2.31 (0.96, 5.32)
	LMWH (standard dose; extended duration)	-	1.16 (0.49, 2.69)
	Apixaban	0.99 (0.77, 1.28)*	0.82 (0.53, 1.25)
	VKA	1.58 (1.33, 1.87)*	1.94 (1.23, 3.06)
	UFH	1.39 (1.08, 1.80)*	1.76 (0.89, 3.38)
	Fondaparinux + AES	-	1.97 (1.02, 3.71)
	LMWH (standard dose; standard duration) + AES	-	2.43 (0.96, 7.27)
	LMWH (low dose; standard duration) + AES	-	3.17 (1.21, 9.19)
	LMWH high dose; standard duration) + AES	-	4.27 (1.86, 9.50)
	UFH + AES	-	2.88 (0.86, 10.61)
Versus AES (length unspecified)	Dabigatran	-	0.28 (0.13, 0.56)
	IPCD (length unspecified)	0.64 (0.29, 1.42)	0.68 (0.32, 1.23)
	Foot pump	-	0.22 (0.05, 0.82)
	Foot pump + AES	-	0.62 (0.29, 1.46)
	Rivaroxaban	-	0.13 (0.05, 0.28)
	Aspirin	-	0.46 (0.16, 1.12)
	LMWH (standard dose; extended duration)	-	0.23 (0.08, 0.59)
	Apixaban	-	0.16 (0.07, 0.34)
	VKA	-	0.39 (0.16, 0.82)
	UFH	-	0.35 (0.12, 0.84)
	Fondaparinux + AES	0.26 (0.11, 0.67)	0.39 (0.17, 0.76)
	LMWH (standard dose; standard duration) + AES	0.58 (0.40, 0.83)	0.48 (0.29, 0.93)
	LMWH (low dose; standard duration) + AES	0.72 (0.53, 0.98)	0.63 (0.32, 1.21)
	LMWH high dose; standard duration) + AES	-	0.87 (0.34, 1.70)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	UFH + AES	-	0.57 (0.23, 1.47)
Versus Dabigatran	IPCD (length unspecified)	-	2.39 (1.22, 4.66)
	Foot pump	-	0.79 (0.18, 2.76)
	Foot pump + AES	-	2.20 (0.79, 7.17)
	Rivaroxaban	-	0.47 (0.25, 0.79)
	Aspirin	-	1.63 (0.66, 3.73)
	LMWH (standard dose; extended duration)	-	0.82 (0.34, 1.86)
	Apixaban	-	0.58 (0.33, 0.97)
	VKA	-	1.37 (0.72, 2.51)
	UFH	-	1.24 (0.54, 2.65)
	Fondaparinux + AES	-	1.39 (0.66, 2.76)
	LMWH (standard dose; standard duration) + AES	-	1.71 (0.68, 5.04)
	LMWH (low dose; standard duration) + AES	-	2.23 (0.85, 6.41)
	LMWH high dose; standard duration) + AES	-	3.01 (1.23, 6.91)
	UFH + AES	-	2.02 (0.61, 7.35)
Versus IPCD (length unspecified)	Foot pump	-	0.33 (0.07, 1.21)
	Foot pump + AES	-	0.91 (0.36, 2.87)
	Rivaroxaban	-	0.20 (0.09, 0.40)
	Aspirin	-	0.68 (0.25, 1.68)
	LMWH (standard dose; extended duration)	-	0.34 (0.13, 0.85)
	Apixaban	-	0.24 (0.12, 0.48)
	VKA	-	0.57 (0.26, 1.24)
	UFH	-	0.52 (0.20, 1.28)
	Fondaparinux + AES	-	0.58 (0.26, 1.26)
	LMWH (standard dose; standard duration) + AES	-	0.70 (0.33, 1.99)
	LMWH (low dose; standard duration) + AES	-	0.93 (0.39, 2.55)
	LMWH high dose; standard duration) + AES	-	1.26 (0.49, 3.00)
	UFH + AES	-	0.84 (0.28, 2.90)
Versus foot pump	Foot pump + AES	-	2.80 (0.62, 17.30)
	Rivaroxaban	-	0.59 (0.16, 2.65)
	Aspirin	-	2.06 (0.46, 10.59)
	LMWH (standard dose; extended duration)	-	1.04 (0.24, 5.28)
	Apixaban	-	0.73 (0.20, 3.27)
	VKA	-	1.73 (0.45, 8.09)
	UFH	-	1.57 (0.37, 7.75)
	Fondaparinux + AES	-	1.75 (0.45, 8.29)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (standard dose; standard duration) + AES	-	2.18 (0.52, 12.54)
	LMWH (low dose; standard duration) + AES	-	2.83 (0.66, 16.01)
	LMWH high dose; standard duration) + AES	-	3.81 (0.90, 19.29)
	UFH + AES	-	2.57 (0.51, 17.00)
Versus foot pump + AES	Rivaroxaban	-	0.21 (0.06, 0.63)
	Aspirin	-	0.74 (0.19, 2.29)
	LMWH (standard dose; extended duration)	-	0.37 (0.09, 1.24)
	Apixaban	-	0.26 (0.08, 0.76)
	VKA	-	0.62 (0.18, 1.77)
	UFH	-	0.56 (0.14, 1.76)
	Fondaparinux + AES	-	0.63 (0.19, 1.75)
	LMWH (standard dose; standard duration) + AES	0.94 (0.73, 1.21)	0.77 (0.42, 1.48)
	LMWH (low dose; standard duration) + AES	-	1.01 (0.39, 2.44)
	LMWH high dose; standard duration) + AES	-	1.39 (0.38, 3.64)
	UFH + AES	-	0.92 (0.34, 2.33)
Versus Rivaroxaban	Aspirin	-	3.47 (1.53, 7.98)
	LMWH (standard dose; extended duration)	-	1.74 (0.74, 4.22)
	Apixaban	-	1.24 (0.71, 2.25)
	VKA	-	2.91 (1.54, 5.91)
	UFH	-	2.64 (1.18, 6.17)
	Fondaparinux + AES	-	2.96 (1.40, 6.43)
	LMWH (standard dose; standard duration) + AES	-	3.67 (1.34, 11.97)
	LMWH (low dose; standard duration) + AES	-	4.78 (1.72, 15.07)
	LMWH high dose; standard duration) + AES	-	6.43 (2.61, 16.07)
	UFH + AES	-	4.35 (1.24, 17.22)
Versus Aspirin	LMWH (standard dose; extended duration)	-	0.50 (0.17, 1.47)
	Apixaban	-	0.36 (0.15, 0.86)
	VKA	-	0.84 (0.33, 2.22)
	UFH	-	0.76 (0.26, 2.25)
	Fondaparinux + AES	-	0.85 (0.32, 2.34)
	LMWH (standard dose; standard duration) + AES	-	1.04 (0.37, 3.85)
	LMWH (low dose; standard duration) + AES	-	1.37 (0.45, 4.90)

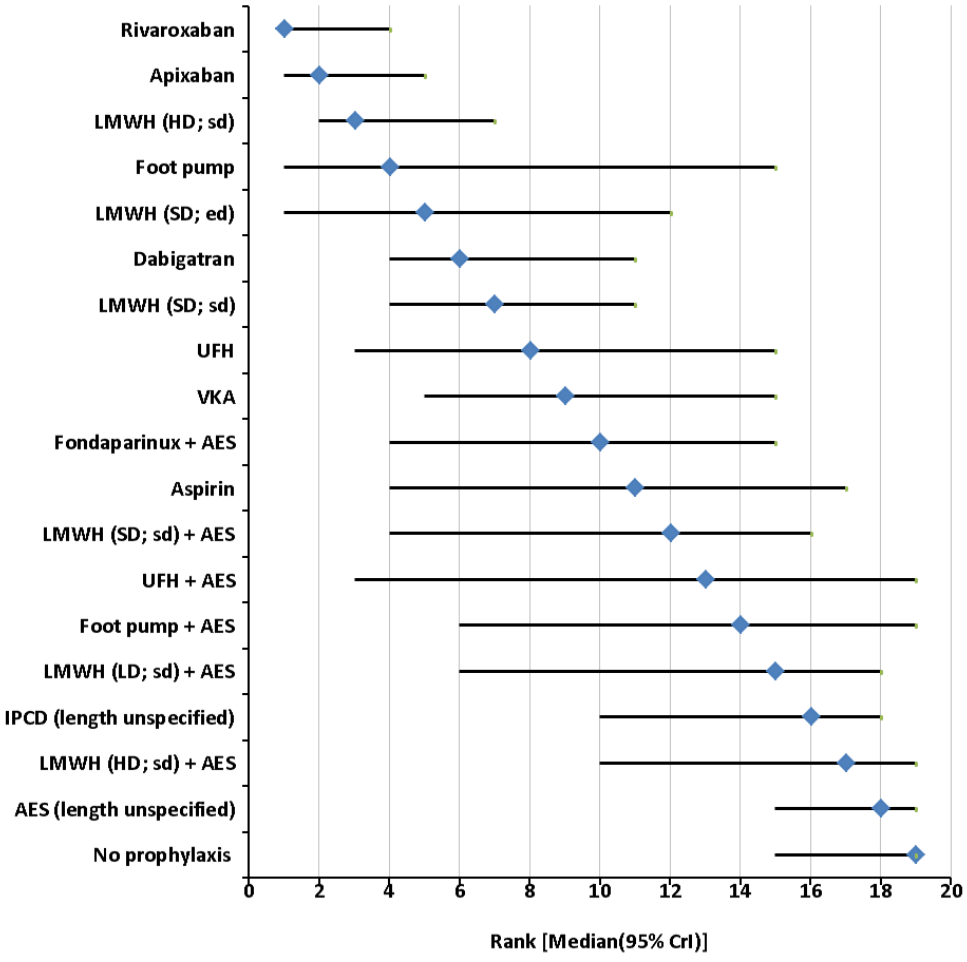
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH high dose; standard duration) + AES	-	1.85 (0.62, 5.60)
	UFH + AES	-	1.24 (0.34, 5.42)
Versus LMWH (standard dose; extended duration)	Apixaban	-	0.71 (0.30, 1.69)
	VKA	-	1.67 (0.65, 4.43)
	UFH	-	1.52 (0.52, 4.47)
	Fondaparinux + AES	-	1.70 (0.63, 4.61)
	LMWH (standard dose; standard duration) + AES	-	2.09 (0.68, 7.77)
	LMWH (low dose; standard duration) + AES	-	2.73 (0.86, 9.91)
	LMWH high dose; standard duration) + AES	-	3.69 (1.22, 11.11)
	UFH + AES	-	2.49 (0.64, 10.94)
Versus Apixaban	VKA	-	2.35 (1.29, 4.42)
	UFH	-	2.14 (0.97, 4.67)
	Fondaparinux + AES	-	2.39 (1.25, 4.54)
	LMWH (standard dose; standard duration) + AES	-	2.96 (1.13, 9.12)
	LMWH (low dose; standard duration) + AES	-	3.85 (1.43, 11.47)
	LMWH high dose; standard duration) + AES	-	5.19 (2.26, 11.67)
	UFH + AES	-	3.49 (1.02, 13.17)
Versus VKA	UFH	-	0.91 (0.40, 1.99)
	Fondaparinux + AES	-	1.01 (0.47, 2.18)
	LMWH (standard dose; standard duration) + AES	-	1.24 (0.49, 3.95)
	LMWH (low dose; standard duration) + AES	-	1.62 (0.60, 5.06)
	LMWH high dose; standard duration) + AES	-	2.20 (0.88, 5.40)
	UFH + AES	-	1.47 (0.44, 5.73)
Versus UFH	Fondaparinux + AES	-	1.12 (0.45, 2.81)
	LMWH (standard dose; standard duration) + AES	-	1.37 (0.48, 4.98)
	LMWH (low dose; standard duration) + AES	-	1.80 (0.60, 6.29)
	LMWH high dose; standard duration) + AES	-	2.42 (0.87, 6.89)
	UFH + AES	-	1.62 (0.45, 7.00)
Versus Fondaparinux + AES	LMWH (standard dose; standard duration) + AES	-	1.23 (0.51, 3.73)
	LMWH (low dose; standard duration) + AES	-	1.61 (0.63, 4.71)
	LMWH high dose; standard duration) + AES	2.18 (1.58, 3.00)	2.17 (1.26, 3.79)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	UFH + AES	-	1.46 (0.45, 5.43)
Versus LMWH (standard dose; standard duration) + AES	LMWH (low dose; standard duration) + AES	1.24 (0.83, 1.85)	1.31 (0.61, 2.48)
	LMWH high dose; standard duration) + AES	-	1.81 (0.55, 3.92)
	UFH + AES	-	1.19 (0.54, 2.35)
Versus LMWH (low dose; standard duration) + AES	LMWH high dose; standard duration) + AES	-	1.37 (0.43, 3.45)
	UFH + AES	-	0.91 (0.33, 2.51)
Versus LMWH (high dose; standard duration) + AES	UFH + AES	-	0.66 (0.22, 2.60)

** Intervention and comparison have been switched in Review Manager*

Figure 834 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 19 different interventions being evaluated.

Figure 834: Rank order for interventions based the relative risk of experiencing DVT



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 352 compared with 350 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 51 reported. This corresponds well to the total number of trial arms, 51. The DIC statistics were as follows in Table 250. The between trial standard deviation in the random effects analysis was 0.24 (95% CI 0.09 to 0.56). On evaluating inconsistency by comparing risk ratios, three inconsistencies were identified. Firstly, the NMA estimated risk ratio for VKA compared to LMWH at a high dose and standard duration (1.94 [1.23, 3.06]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (1.58 [1.33, 1.87]). Secondly, the NMA estimated risk ratio for dabigatran versus no prophylaxis (0.25 [0.14, 0.42]) lay outside of the confidence interval of the risk ration estimated for the direct comparison (0.42 [0.29, 0.63]). Lastly, the NMA estimated risk ratio for dabigatran compared to LMWH at a standard dose and standard duration (0.97 [0.64, 1.52]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (1.29 [1.09, 1.53]) An inconsistency model was run and the DIC statistics were as follows in Table 250. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 250: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – DVT

	DIC	ResDev
Consistency model	352.435	51
Inconsistency model	357.161	51

M.2.3.2 Pulmonary embolism

Included studies

19 studies were identified as reporting on major bleeding outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 12 studies involving 13 treatments were included in the network for PE. The network can be seen in **Figure 835**and the trial data for each of the studies included in the NMA are presented in **Table 251**.

Figure 835: Network diagram for PE

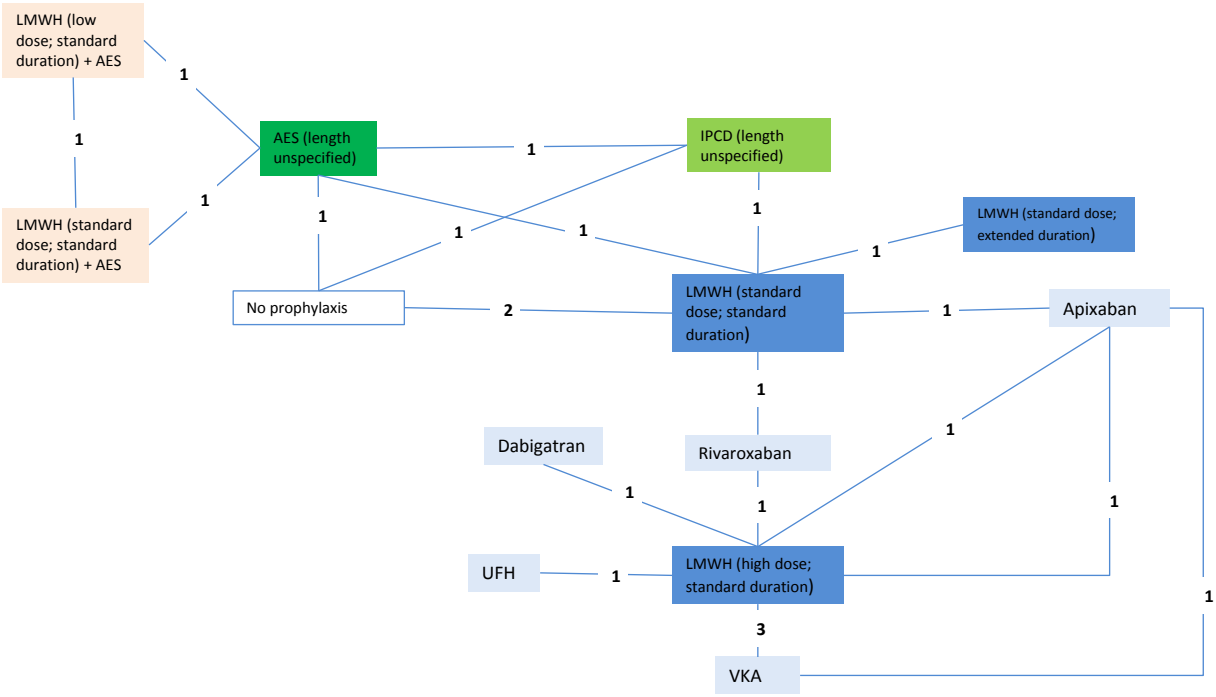


Table 251: Study data for PE network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Intervention 3	Comparison		Intervention 1		Intervention 2		Intervention 3	
					N	NA	N	NA	N	NA	N	NA
Chin 2009 [177]	No prophylaxis	LMWH (standard dose; standard duration)	AES (length unspecified)	IPCD (length unspecified)	1	110	0	110	1	110	0	110
Lassen 2008 [525]	LMWH (standard dose; standard duration)	Rivaroxaban	-	-	4	1217	0	1201	-	-	-	-
Lassen 2010 [535]	LMWH (standard dose; standard duration)	Apixaban	-	-	1	1449	3	1458	-	-	-	-
Comp 2001 [208]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	-	2	222	0	218	-	-	-	-
Fuji 2008A [328]	AES	LMWH (standard dose; standard duration) + AES	LMWH (low dose; standard duration) + AES	-	1	79	1	74	1	78	-	-
Ginsberg 2009 [792]	Dabigatran	LMWH (high dose; standard duration)	-	-	6	604	5	643	-	-	-	-
Turpie 2009 [956]	Rivaroxaban	LMWH (high dose; standard duration)	-	-	4	1526	8	1508	-	-	-	-
Lassen 2009 [536]	Apixaban	LMWH (high dose; standard duration)	-	-	15	1599	10	1596	-	-	-	-
Lassen 2007[532]	Apixaban	LMWH (high dose; standard duration)	VKA	-	0	208	2	109	0	109	-	-
Fitzgerald 2001 [308]	LMWH (high dose; standard duration)	VKA	-	-	0	173	1	176	-	-	-	-
Leclerc 1996 [543]	LMWH (high dose; standard duration)	VKA	-	-	1	206	3	211	-	-	-	-
Colwell 1995D [205]	LMWH (high dose; standard duration)	UFH	-	-	0	145	2	143	-	-	-	-

N; number of events, NA; number analysed

NMA results - PE

Table 252 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 252: Risk ratios for PE

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	LMWH (standard dose; standard duration)	0.33 (0.01, 8.09)	0.20 (0.00, 8.57)
	AES (length unspecified)	1.00 (0.06, 15.79)	0.98 (0.04, 24.95)
	IPCD (length unspecified)	0.33 (0.01, 8.09)	0.20 (0.00, 8.53)
	Dabigatran	-	0.47 (0.00, 56.97)
	Rivaroxaban	-	0.08 (0.00, 6.65)
	Apixaban	-	0.52 (0.00, 36.43)
	LMWH (standard duration; extended duration)	-	0.02 (0.00, 3.86)
	LMWH (standard dose; standard duration) + AES	-	1.00 (0.01, 199.30)
	LMWH (low dose; standard duration) + AES	-	0.97 (0.01, 167.70)
	LMWH (high dose; standard duration)	-	0.37 (0.00, 30.66)
	VKA	-	0.63 (0.00, 64.93)
	UFH	-	1.79 (0.00, 625.00)
Versus LMWH (standard dose; standard duration)	AES (length unspecified)	3.00 (0.12, 72.85)*	5.00 (0.12, 3120.00)
	IPCD (length unspecified)	-	0.98 (0.00, 791.60)
	Dabigatran	-	2.45 (0.11, 52.27)
	Rivaroxaban	0.11 (0.01, 2.03)*	0.45 (0.04, 3.62)
	Apixaban	6.00 (0.72, 49.81)*	2.59 (0.32, 21.68)
	LMWH (standard duration; extended duration)	0.20 (0.01, 4.22)	0.11 (0.00, 3.33)
	LMWH (standard dose; standard duration) + AES	-	6.04 (0.02, 9283.00)
	LMWH (low dose; standard duration) + AES	-	5.68 (0.02, 8979.00)
	LMWH (high dose; standard duration)	-	1.90 (0.20, 18.92)
	VKA	-	3.23 (0.20, 52,24)
	UFH	-	9.06 (0.12, 1640.00)
Versus AES (length unspecified)	IPCD (length unspecified)	0.33 (0.01, 8.09)	0.20 (0.00, 8.36)
	Dabigatran	-	0.48 (0.00, 48.08)
	Rivaroxaban	-	0.08 (0.00, 6.65)
	Apixaban	-	0.52 (0.00, 32.84)
	LMWH (standard duration; extended duration)	-	0.01 (0.00, 3.86)
	LMWH (standard dose; standard duration) + AES	1.07 (0.07, 16.76)	1.04 (0.02, 61.02)

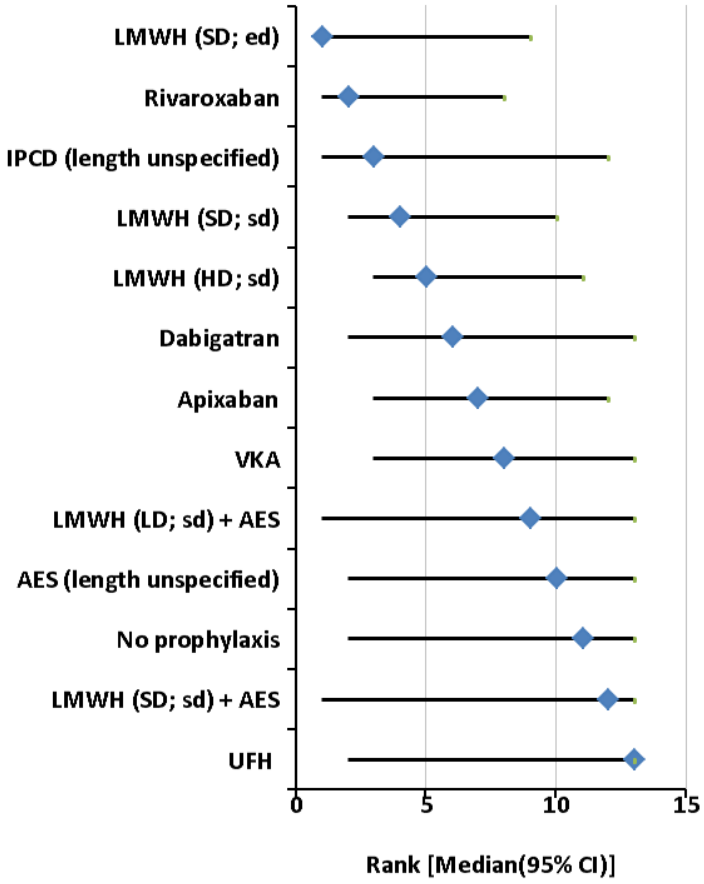
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (low dose; standard duration) + AES	1.01 (0.06, 15.91)	1.00 (0.02, 54.60)
	LMWH (high dose; standard duration)	-	0.37 (0.00, 27.68)
	VKA	-	0.64 (0.00, 52.48)
	UFH	-	1.95 (0.00, 372.20)
Versus IPCD (length unspecified)	Dabigatran	-	2.51 (0.00, 3274.00)
	Rivaroxaban	-	0.45 (0.00, 447.00)
	Apixaban	-	2.68 (0.00, 2584.00)
	LMWH (standard duration; extended duration)	-	0.08 (0.00, 189.20)
	LMWH (standard dose; standard duration) + AES	-	5.96 (0.02, 9804.00)
	LMWH (low dose; standard duration) + AES	-	5.55 (0.02, 8305.00)
	LMWH (high dose; standard duration)	-	1.96 (0.00, 2030.00)
	VKA	-	3.31 (0.00, 3828.00)
	UFH	-	10.55 (0.00, 26060.00)
Versus Dabigatran	Rivaroxaban	-	0.18 (0.01, 2.80)
	Apixaban	-	1.07 (0.08, 14.05)
	LMWH (standard duration; extended duration)	-	0.04 (0.00, 4.37)
	LMWH (standard dose; standard duration) + AES	-	2.40 (0.01, 7128.00)
	LMWH (low dose; standard duration) + AES	-	2.28 (0.00, 6754.00)
	LMWH (high dose; standard duration)	0.78 (0.24, 2.55)	0.79 (0.10, 6.71)
	VKA	-	1.31 (0.09, 21.28)
	UFH	-	3.52 (0.05, 769.80)
Versus Rivaroxaban	Apixaban	-	5.92 (0.73, 64.04)
	LMWH (standard duration; extended duration)	-	0.23 (0.00, 16.74)
	LMWH (standard dose; standard duration) + AES	-	14.28 (0.03, 35160.00)
	LMWH (low dose; standard duration) + AES	-	13.27 (0.03, 32390.00)
	LMWH (high dose; standard duration)	2.02 (0.61, 6.71)	4.23 (0.73, 37.87)
	VKA	-	7.32 (0.65, 116.30)
	UFH	-	20.27 (0.35, 4323.00)
Versus Apixaban	LMWH (standard duration; extended duration)	-	0.04 (0.00, 2.29)
	LMWH (standard dose; standard duration) + AES	-	2.21 (0.01, 4884.00)
	LMWH (low dose; standard duration) + AES	-	2.11 (0.01, 4578.00)
	LMWH (high dose; standard duration)	0.44 (0.18, 1.06)	0.72 (0.17, 3.46)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	VKA	-	1.22 (0.15, 10.54)
	UFH	-	3.25 (0.06, 574.10)
Versus LMWH (standard dose; extended duration)	LMWH (standard dose; standard duration) + AES	-	79.99 (0.07, 785700.00)
	LMWH (low dose; standard duration) + AES	-	74.78 (0.06, 724000.00)
	LMWH (high dose; standard duration)	-	19.13 (0.30, 21100.00)
	VKA	-	33.28 (0.38, 43380.00)
	UFH	-	111.30 (0.35, 330100.00)
Versus LMWH (standard dose; standard duration) + AES	LMWH (low dose; standard duration) + AES	0.95 (0.06, 14.89)	0.95 (0.01, 47.24)
	LMWH (high dose; standard duration)	-	0.32 (0.00, 99.27)
	VKA	-	0.56 (0.00, 140.60)
	UFH	-	1.97 (0.00, 218.00)
Versus LMWH (low dose; standard duration) + AES	LMWH (high dose; standard duration)	-	0.34 (0.00, 135.20)
	VKA	-	0.59 (0.00, 249.50)
	UFH	-	1.94 (0.00, 1050.00)
Versus LMWH (high dose; standard duration)	VKA	1.31 (0.30, 5.79)*	1.68 (0.29, 10.18)
	UFH	3.04 (0.12, 74.05)*	4.38 (0.12, 663.70)
Versus VKA	UFH	-	2.61 (0.04, 533. 70)

** Intervention and comparison have been switched in Review Manager*

Figure 836 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 13 different interventions being evaluated.

Figure 836: Rank order for interventions based the relative risk of experiencing PE



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 125 compared with 127 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 32 reported. This corresponds well to the total number of trial arms, 28. The between trial standard deviation in the random effects analysis was 0.67 (95% CI 0.18 to 1.98). No inconsistency was identified between the direct RR and NMA results. The DIC statistics were as follows in **Table 253**.

Table 253: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – PE

	DIC	ResDev
Consistency model	124.870	32
Inconsistency model	125.068	32

M.2.3.3 Major bleeding

Included studies

19 studies were identified as reporting on major bleeding outcomes. All of the studies identified, involving 11 treatments were included in the network for major bleeding. The network can be seen in **Figure 837** and the trial data for each of the studies included in the NMA are presented in **Table 254**.

Figure 837: Network diagram for major bleeding

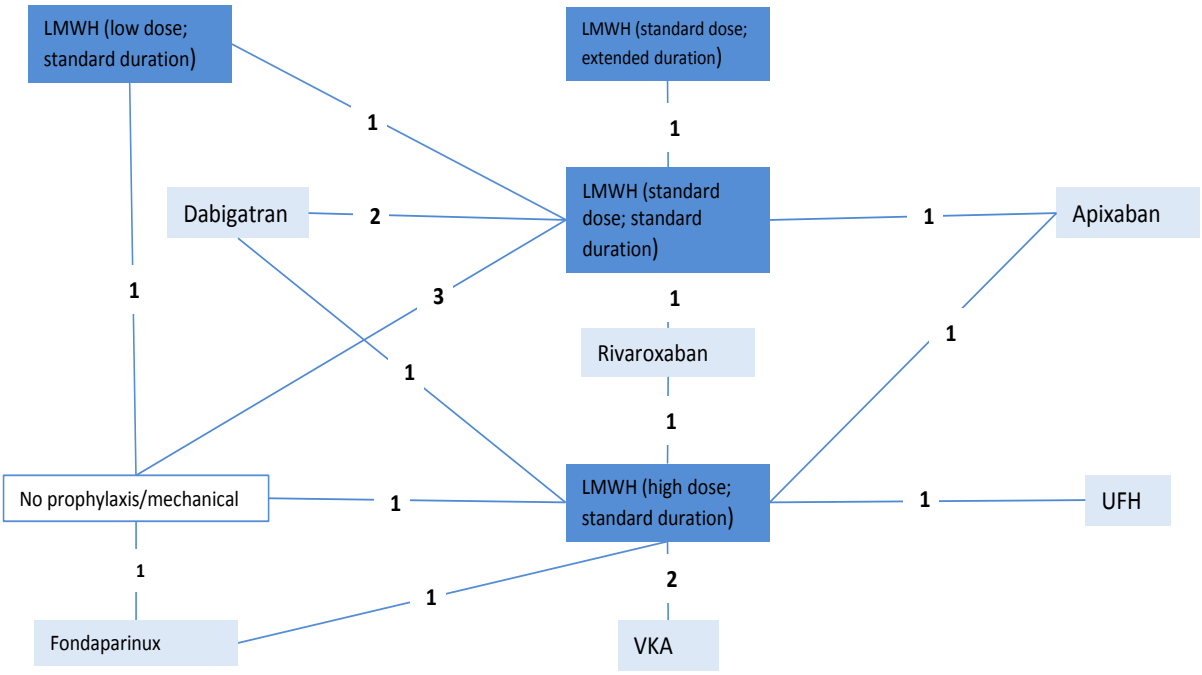


Table 254: Study data for major bleeding network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
				N	NA	N	NA	N	NA
Fuji 2008A[328]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	LMWH (low dose; standard duration)	4	89	1	91	0	89
Chin 2009 [177]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	-	0	110	2	110	-	-
Blanchard 1999A [106]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	-	0	63	1	67	-	-
Leclerc 1992 [543]	No prophylaxis/ mechanical	LMWH (high dose; standard duration)	-	1	65	0	66	-	-
Fuji 2008 [325]	No prophylaxis/ mechanical	Fondaparinux	-	1	87	1	84	-	-
Fuji 2010[320]	No prophylaxis/ mechanical	Dabigatran	-	1	124	4	129	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
Lassen 2010 [535]	LMWH (standard dose; standard duration)	Apixaban	-	14	1508	9	1501	-	-
Eriksson 2007 [293]	LMWH (standard dose; standard duration)	Dabigatran	-	9	694	10	679	-	-
Mirdamidi 2014 [641]	LMWH (standard dose; standard duration)	Dabigatran	-	2	45	3	45	-	-
Lassen 2008 [525]	LMWH (standard dose; standard duration)	Rivaroxaban	-	17	1277	21	1254	-	-
Comp 2001 [208]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	1	221	0	217	-	-
Bauer 2001[78]	LMWH (high dose; standard duration)	Fondaparinux	-	1	517	11	517	-	-
Lassen 2009 [536]	LMWH (high dose; standard duration)	Apixaban	-	22	1588	11	1596	-	-
Lassen 2007[532]	LMWH (high dose; standard duration)	Apixaban	VKA	0	149	4	305	0	151
Ginsberg 2009 [792]	LMWH (high dose; standard duration)	Dabigatran	-	12	868	5	857	-	-
Turpie 2009 [956]	LMWH (high dose; standard duration)	Rivaroxaban	-	16	1564	27	1584	-	-
Colwell 1995D [205]	LMWH (high dose; standard duration)	UFH	-	3	228	3	225	-	-
Fitzgerald 2001 [308]	LMWH (high dose; standard	VKA	-	9	173	4	176	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
	duration)								
Leclerc 1996 [544]	LMWH (high dose; standard duration)	VKA	-	6	336	5	334	-	-

N; number of events, NA; number analysed

NMA results- major bleeding

Table 255 summarises the results of the conventional meta-analyses in terms of odd ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of odd ratios for every possible treatment comparison. Relative risks were not calculated for this outcome as data was only available for non-surgical site bleeding (intracranial haemorrhage + gastrointestinal bleeding) from the observational study used as the source of baseline risk.[450]

Table 255: Odd ratios for major bleeding

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no mechanical prophylaxis	LMWH (standard dose; standard duration)	0.98 (0.28, 3.40)	1.09 (0.34, 3.75)
	LMWH (high dose; standard duration)	0.32 (0.01, 8.08)	1.02 (0.24, 3.97)
	Fondaparinux	1.04 (0.06, 16.84)	6.74 (0.79, 76.28)
	LMWH (low dose; standard duration)	0.11 (0.01, 2.00)	0.08 (0.00, 1.76)
	Apixaban	-	0.79 (0.18, 3.99)
	Dabigatran	-	1.08 (0.29, 4.36)
	Rivaroxaban	-	1.55 (0.32, 7.35)
	LMWH (standard dose; extended duration)	-	0.21 (0.00, 10.41)
	UFH	-	1.03 (0.07, 13.19)
	VKA		0.52 (0.08, 2.89)
Versus LMWH (standard dose; standard duration)	LMWH (high dose; standard duration)	-	0.95 (0.27, 2.63)
	Fondaparinux	-	6.18 (0.73, 66.87)
	LMWH (low dose; standard duration)	0.34 (0.01, 8.38)*	0.08 (0.00, 1.62)
	Apixaban	0.64 (0.28, 1.49)*	0.72 (0.23, 2.50)
	Dabigatran	1.21 (0.54, 2.72)*	0.99 (0.35, 2.86)
	Rivaroxaban	1.26 (0.66, 2.40)*	1.43 (0.41, 4.45)
	LMWH (standard dose; extended duration)	0.34 (0.01, 8.34)	0.19 (0.00, 7.62)
	UFH	-	0.95 (0.07, 10.30)
	VKA	-	0.48 (0.09, 2.05)
Versus	Fondaparinux	11.22 (1.44, 87.20)*	6.57 (1.07, 62.67)

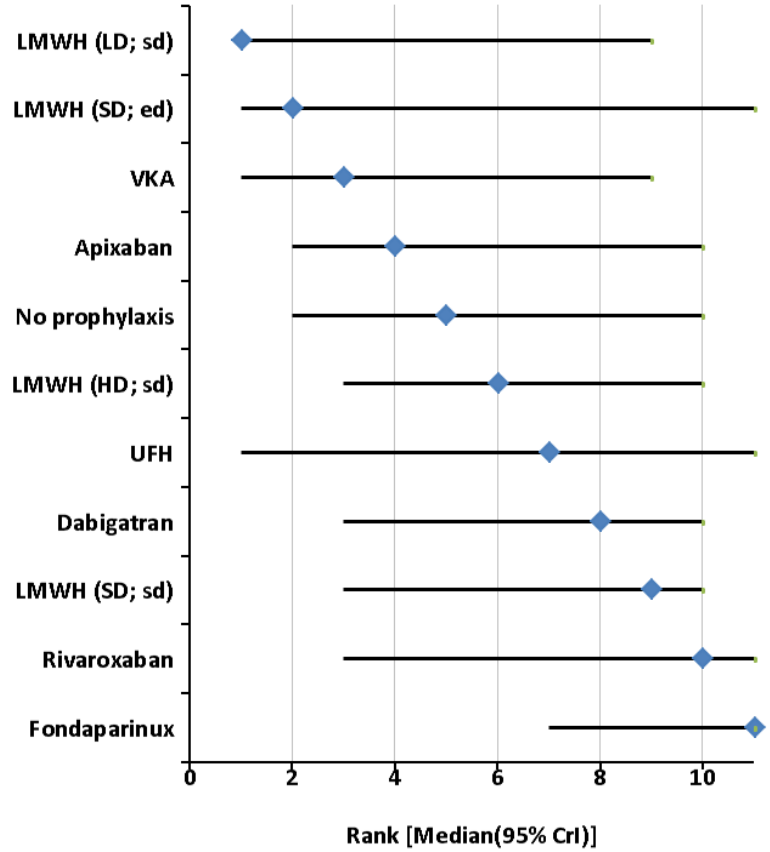
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
LMWH (high dose; standard duration)	LMWH (low dose; standard duration)	-	0.08 (0.00, 2.09)
	Apixaban	0.61 (0.31, 1.19)*	0.77 (0.30, 2.70)
	Dabigatran	0.42 (0.15, 1.19)*	1.05 (0.35, 3.99)
	Rivaroxaban	1.68 (0.90, 3.13)*	1.50 (0.49, 5.32)
	LMWH (standard dose; extended duration)	-	0.20 (0.00, 10.27)
	UFH	1.01 (0.20, 5.08)*	1.01 (0.11, 8.95)
	VKA	0.61 (0.28, 1.37)*	0.51 (0.15, 1.57)
Versus Fondaparinux	LMWH (low dose; standard duration)	-	0.01 (0.00, 0.48)
	Apixaban	-	0.12 (0.01, 1.08)
	Dabigatran	-	0.16 (0.01, 1.44)
	Rivaroxaban	-	0.23 (0.02, 2.05)
	LMWH (standard dose; extended duration)	-	0.03 (0.00, 2.25)
	UFH	-	0.15 (0.01, 2.68)
	VKA	-	0.08 (0.01, 0.65)
Versus LMWH (low dose; standard duration)	Apixaban	-	9.71 (0.37, 5795.00)
	Dabigatran	-	13.03 (0.54, 7827.00)
	Rivaroxaban	-	18.67 (0.71, 11130.00)
	LMWH (standard dose; extended duration)	-	2.64 (0.00, 3297.00)
	UFH	-	13.32 (0.24, 9936.00)
	VKA		6.30 (0.20, 3743.00)
Versus Apixaban	Dabigatran	-	1.36 (0.33, 5.46)
	Rivaroxaban	-	1.98 (0.41, 7.59)
	LMWH (standard dose; extended duration)	-	0.26 (0.00, 12.79)
	UFH	-	1.31 (0.10, 13.72)
	VKA	0.22 (0.01, 4.13)*	0.66 (0.12, 2.53)
Versus Dabigatran	Rivaroxaban	-	1.45 (0.32, 5.66)
	LMWH (standard dose; extended duration)	-	0.19 (0.00, 9.01)
	UFH	-	0.96 (0.07, 10.66)
	VKA		0.48 (0.08, 2.24)
Versus Rivaroxaban	LMWH (standard dose; extended duration)	-	0.13 (0.00, 6.77)
	UFH	-	0.67 (0.05, 7.67)
	VKA		0.33 (0.06, 1.59)
Versus LMWH (standard dose; extended duration)	UFH	-	5.25 (0.05, 3299.00)
	VKA		2.51 (0.04, 1310.00)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus UFH	VKA		0.50 (0.04, 5.92)

** Intervention and comparison have been switched in Review Manager*

Figure 838 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 11 different interventions being evaluated.

Figure 838: Rank order for interventions based the relative risk of experiencing major bleeding



SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 196 compared with 197 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 41 reported. This corresponds well to the total number of trial arms, 40. The between trial standard deviation in the random effects analysis was 0.54 (95% CI 0.19 to 1.28). No inconsistency was identified between the direct RR and NMA results. The DIC statistics were as follows in **Table 256**.

Table 256: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – Major bleeding

	DIC	TotResDev
Consistency model	196.222	42
Inconsistency model	199.124	42

M.2.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 26 and Appendix H, deciding upon the most clinical and cost effective prophylaxis intervention in patients undergoing elective knee replacement surgery is challenging. In order to overcome the difficulty of interpreting the conclusions from numerous separate comparisons, network meta-analysis of the direct evidence was performed. The findings of the NMA were used to facilitate the guideline committee in decision-making when developing recommendations.

Our analyses were divided into three critical outcomes. 23 studies informed the DVT network where 19 different individual or combination treatments were evaluated including three mechanical interventions, nine pharmacological interventions, and six interventions that combined both mechanical and pharmacological prophylaxis. 12 studies informed the PE network of 13 different treatments, including two mechanical interventions, seven pharmacological interventions, and two interventions that combined both mechanical and pharmacological prophylaxis. The major bleeding network included 19 studies evaluating 11 treatments, nine of which were pharmacological as for this outcome any mechanical prophylaxis measures were combined with the no prophylaxis intervention as it is believed that mechanical prophylaxis has no associated bleeding risk.

In the DVT network, the top three interventions were rivaroxaban, apixaban and LMWH at a high dose for a standard duration. The bottom three interventions were no prophylaxis, AES (length unspecified) and LMWH at a high dose for a standard duration plus AES. The highest ranked combination of mechanical and pharmacological prophylaxis was fondaparinux plus AES in tenth place. The four other combination interventions of mechanical plus pharmacological interventions ranked from 15 to 17. There was considerable uncertainty about the estimates with the credible intervals for some of the interventions being quite wide. The top three interventions spanned up to 7 rankings.

In the PE network, the top three interventions were LMWH at a standard dose for an extended duration, rivaroxaban, and IPCD (length unspecified). The bottom three interventions were UFH, LMWH at a standard dose for a standard duration plus AES andno prophylaxis. There was also considerable uncertainty in the PE network with wide credible intervals for a majority of the interventions, for example for LMWH at a low dose for a standard duration plus AES and LMWH at a standard dose for a standard duration plus AES spanning all 13 ranking positions.

In the major bleeding network the highest ranked intervention was LMWH at a low dose for a standard duration, followed LMWH at a standard dose for an extended duration then VKA. The bottom three interventions were fondaparinux, rivaroxaban and LMWH at a standard dose for a standard duration. There was a lot of uncertainty within the major bleeding network with very wide credible intervals for all of the interventions spanning almost all ranking positions.

In summary, the three outcomes chosen for analyses were considered to be among the most critical for assessing clinical effectiveness of different VTE prophylaxis strategies. All three networks seemed to fit well, as demonstrated by residual deviance and no obvious inconsistency found in the networks. However the credible intervals around the ranking of treatments in all three networks were wide suggesting considerable uncertainty about these results.

M.2.5 Conclusion

This analysis allowed us to combine findings from many different comparisons presented in the review even when direct comparative data was lacking.

The guideline committee and orthopaedic subgroup noted the wide credible intervals particularly for the PE and major bleeding network meta-analyses. They both also noted that even with the high levels of uncertainty, interventions such as rivaroxaban and LMWH present possible clinical effectiveness in terms of the outcomes of DVT (symptomatic and asymptomatic) and PE.

For details of the rationale and discussion leading to recommendations, please refer to the section linking the evidence to the recommendations (section 27.6, chapter 27).

M.2.6 WinBUGS codes

M.2.6.1 WinBUGS code for number of patients with DVT (symptomatic and asymptomatic)

```
#Random effects model for multi-arm trials (any number of arms)

model{

for(i in 1:NS){

  w[i,1] <-0

  delta[i,t[i,1]]<-0

  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines

  for (k in 1:na[i]){

    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood

    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model

#Deviance residuals for data i

  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

   }

  sdev[i]<- sum(dev[i,1:na[i]])

  for (k in 2:na[i]){

# trial-specific LOR distributions

    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions

    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions

#adjustment, multi-arm RCTs

    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])

# cumulative adjustment for multi-arm trials

    sw[i,k] <-sum(w[i,1:k-1])/(k-1)

   }
```

```
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)       # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[16] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 120639
a <- 16891
for (k in 1:15){       # treatments below 16
  logit(v[k]) <- logit(v[16]) - lor[k,16]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

for (k in 17:NT){    # treatments above 16
  logit(v[k]) <- logit(v[16]) + lor[16,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

rr[16] <- v[16]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
```

```
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lor[c,k] <- d[k] - d[c]
    log(or[c,k]) <- lor[c,k]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.


list(NT=19, NS=23,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: general physical health indicators
m.tau= -1.26, sd.tau=1.25 )

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 24 110 6 110 14 110 9 110 NA NA 1 2 4 6 NA 4
 37 64 11 65 NA NA NA NA NA NA 1 3 NA NA NA 2
 57 101 23 96 NA NA NA NA NA NA 1 5 NA NA NA 2
 19 32 5 28 NA NA NA NA NA NA 1 7 NA NA NA 2
 192 685 182 675 NA NA NA NA NA NA 2 5 NA NA NA 2
 16 67 34 63 NA NA NA NA NA NA 2 6 NA NA NA 2
 0.5 15 4.5 16 NA NA NA NA NA NA 2 8 NA NA NA 2
```

14 112 3 102 18 110 NA NA NA NA 2 9 10 NA NA 3

160 878 79 824 NA NA NA NA NA NA 2 9 NA NA NA 2

37 144 33 155 NA NA NA NA NA NA 2 11 NA NA NA 2

243 997 142 971 NA NA NA NA NA NA 2 12 NA NA NA 2

158 643 181 604 NA NA NA NA NA NA 3 5 NA NA NA 2

86 959 61 965 NA NA NA NA NA NA 3 9 NA NA NA 2

15 109 21 208 29 109 NA NA NA NA 3 12 15 NA NA 3

92 1122 89 1142 NA NA NA NA NA NA 3 12 NA NA NA 2

44 173 79 176 NA NA NA NA NA NA 3 13 NA NA NA 2

76 206 109 211 NA NA NA NA NA NA 3 13 NA NA NA 2

56 145 77 143 NA NA NA NA NA NA 3 14 NA NA NA 2

19 74 5 74 NA NA NA NA NA NA 4 15 NA NA NA 2

48 79 25 74 34 78 NA NA NA NA 4 16 17 NA NA 3

57 99 48 89 NA NA NA NA NA NA 8 16 NA NA NA 2

45 361 98 361 NA NA NA NA NA NA 15 18 NA NA NA 2

21 91 25 93 NA NA NA NA NA NA 16 19 NA NA NA 2

END

list(
d=c(NA,0,0,0,0,0,0,0,1,2,3,4,2,3,1,0,2,1,-2), # one for each treatment
sd.sq=1,
mu=c(0,0,3,0,0, 0,2,0,-1,0, 4,0,3,1,0, 0, 2,1,3, 2,0, 1, 2))

list(
d=c(NA,1,0,2,0,3,0,0,1,2,3,4,2,3,1,0,1,3,-3), # one for each treatment
sd.sq=0.1,
mu=c(0,2,1,0,-2, 0,3,0,4,0, 2,0,1,3,0, 0, 2,1,3,1,0, 0, -1))

list(
d=c(NA,0,0,0,0,0,0,0,1,2,3,4,2,3,1,0,0,1,2), # one for each treatment
sd.sq=2,

```
mu=c(0,3,3,0,4, 0,1,0,-2,0, 1,2,0,2,0, 0, 2,1,3,-3,4, 2, 1) )
```

M.2.6.2 WinBUGS code for inconsistency model for number of patients with DVT

```
VTE - inconsistency model - Elective knee DVT
==============================
23 trials
19 treaments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
     }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
```

```
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS
```

Data

```
# DVT
# nt=no. treatments, ns=no. studies
list(nt=19,ns=23, m.tau= -1.26, sd.tau=1.25)

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
24 110 6 110 14 110 9 110 NA NA 1 2 4 6 NA 4
37 64 11 65 NA NA NA NA NA NA 1 3 NA NA NA 2
57 101 23 96 NA NA NA NA NA NA 1 5 NA NA NA 2
19 32 5 28 NA NA NA NA NA NA 1 7 NA NA NA 2
192 685 182 675 NA NA NA NA NA NA 2 5 NA NA NA 2
16 67 34 63 NA NA NA NA NA NA 2 6 NA NA NA 2
0.5 15 4.5 16 NA NA NA NA NA NA 2 8 NA NA NA 2
14 112 3 102 18 110 NA NA NA NA 2 9 10 NA NA 3
160 878 79 824 NA NA NA NA NA NA 2 9 NA NA NA 2
37 144 33 155 NA NA NA NA NA NA 2 11 NA NA NA 2
243 997 142 971 NA NA NA NA NA NA 2 12 NA NA NA 2
158 643 181 604 NA NA NA NA NA NA 3 5 NA NA NA 2
86 959 61 965 NA NA NA NA NA NA 3 9 NA NA NA 2
15 109 21 208 29 109 NA NA NA NA 3 12 15 NA NA 3
92 1122 89 1142 NA NA NA NA NA NA 3 12 NA NA NA 2
```

44 173 79 176 NA NA NA NA NA NA 3 13 NA NA NA 2

76 206 109 211 NA NA NA NA NA NA 3 13 NA NA NA 2

56 145 77 143 NA NA NA NA NA NA 3 14 NA NA NA 2

19 74 5 74 NA NA NA NA NA NA 4 15 NA NA NA 2

48 79 25 74 34 78 NA NA NA NA 4 16 17 NA NA 3

57 99 48 89 NA NA NA NA NA NA 8 16 NA NA NA 2

45 361 98 361 NA NA NA NA NA NA 15 18 NA NA NA 2

21 91 25 93 NA NA NA NA NA NA 16 19 NA NA NA 2

END

INITS

#chain 1

list(sd.sq=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,1),

d = structure(.Data = c(

NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,

```
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0  ),
.Dim = c(18,19))   )

# chain 2
list(sd.sq=1.5,  mu=c(2,1,3,1,2,   0,2,0,-1,3,   2,0,1,3,1,   1,2,-3,2,0,   0,0,-1),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5  ),
.Dim = c(18,19))  )

# chain 3
list(sd.sq=3,  mu=c(2,0.5,3,0.5,2,   -2,2,1,-1,3,    2,1,1,3,1,    1,2,-3,2,1,    1,2,2),
d = structure(.Data = c(
        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
```

```
        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3  ),
.Dim = c(18,19))  )
```

M.2.6.3 WinBUGS code for number of patients with pulmonary embolism (PE)

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  sdev[i]<- sum(dev[i,1:na[i]])
  for (k in 2:na[i]){
```

```
# trial-specific LOR distributions
   delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
   md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
   taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
   w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[9] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 120639
a <- 539
for (k in 1:8){       # treatments below 8
  logit(v[k]) <- logit(v[9]) - lor[k,9]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

for (k in 10:NT){    # treatments above 9
```

```
  logit(v[k]) <- logit(v[9]) + lor[9,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

rr[9] <- v[9]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lor[c,k] <- d[k] - d[c]
    log(or[c,k]) <- lor[c,k]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 4.

list(NT=13, NS=12,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: general physical health indicators
m.tau= -1.26, sd.tau=1.25  )
```

```
r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
1.5 111 0.5 111 1.5 111 0.5 111 NA NA 1 2 3 4 NA 4
4.5 1218 0.5 1202 NA NA NA NA NA NA 2 6 NA NA NA 2
1 1529 7 1528 NA NA NA NA NA NA 2 7 NA NA NA 2
2.5 222 0.5 218 NA NA NA NA NA NA 2 8 NA NA NA 2
1 79 1 74 1 78 NA NA NA NA 3 9 10 NA NA 3
6 604 5 643 NA NA NA NA NA NA 5 11 NA NA NA 2
4 1526 8 1508 NA NA NA NA NA NA 6 11 NA NA NA 2
15 1599 10 1596 NA NA NA NA NA NA 7 11 NA NA NA 2
0.5 209 2.5 110 0.5 110 NA NA NA NA 7 11 12 NA NA 3
0.5 174 1.5 177 NA NA NA NA NA NA 11 12 NA NA NA 2
1 206 3 211 NA NA NA NA NA NA 11 12 NA NA NA 2
0.5 146 1.5 144 NA NA NA NA NA NA 11 13 NA NA NA 2

END

list(
d=c(NA,0,0,0,0,0,0,0,1,2,3,4,2), # one for each treatment
sd.sq=1,
mu=c(0,0,3,0,0, 0,2,0,-1,0, 4,1) )

list(
d=c(NA,1,0,2,0,3,0,0,1,2,3,4,2), # one for each treatment
sd.sq=0.1,
mu=c(0,2,1,0,-2, 0,3,0,4,0, 2,-1) )

list(
d=c(NA,0,0,0,0,0,0,0,1,2,3,4,2), # one for each treatment
sd.sq=2,
mu=c(0,3,3,0,4, 0,1,0,-2,0, 1,0) )
```

M.2.6.4 WinBUGS code for inconsistency model for number of patients with PE

```
VTE - inconsistency model - Elective knee PE
==============================
12 studies
13 treaments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
```

```
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS
```

Data

```
# DVT
# nt=no. treatments, ns=no. studies
list(nt=13,ns=12, m.tau= -1.26, sd.tau=1.25)

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 1.5 111 0.5 111 1.5 111 0.5 111 NA NA 1 2 3 4 NA 4
 4.5 1218 0.5 1202 NA NA NA NA NA NA 2 6 NA NA NA 2
 1 1529 7 1528 NA NA NA NA NA NA 2 7 NA NA NA 2
 2.5 222 0.5 218 NA NA NA NA NA NA 2 8 NA NA NA 2
 1 79 1 74 1 78 NA NA NA NA 3 9 10 NA NA 3
 6 604 5 643 NA NA NA NA NA NA 5 11 NA NA NA 2
 4 1526 8 1508 NA NA NA NA NA NA 6 11 NA NA NA 2
 15 1599 10 1596 NA NA NA NA NA NA 7 11 NA NA NA 2
 0.5 209 2.5 110 0.5 110 NA NA NA NA 7 11 12 NA NA 3
 0.5 174 1.5 177 NA NA NA NA NA NA 11 12 NA NA NA 2
 1 206 3 211 NA NA NA NA NA NA 11 12 NA NA NA 2
 0.5 146 1.5 144 NA NA NA NA NA NA 11 13 NA NA NA 2

END
```

INITS

```
#chain 1
```

```
list(sd.sq=1,  mu=c(2,0,3,0,2,   -2,2,-2,-1,3,   2,-2),
d = structure(.Data = c(
        NA,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0  ),
.Dim = c(12,13))   )

# chain 2
list(sd.sq=1.5,  mu=c(2,1,3,1,2,   0,2,0,-1,3,   2,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5),
.Dim = c(12,13))  )
```

```
# chain 3
list(sd.sq=3,  mu=c(2,0.5,3,0.5,2,   -2,2,1,-1,3,    2,1),
d = structure(.Data = c(
        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3  ),
.Dim = c(12,13))  )
```

M.2.6.5 WinBUGS code for number of patients with major bleeding

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  sdev[i]<- sum(dev[i,1:na[i]])
```

```
  for (k in 2:na[i]){
# trial-specific LOR distributions
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <-sum(w[i,1:k-1])/(k-1)
   }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[2] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 120639
a <- 465
for (k in 1:1){       # treatments below 2
  logit(v[k]) <- logit(v[2]) - lor[k,2]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }
```

```
for (k in 3:NT){    # treatments above 2
  logit(v[k]) <- logit(v[2]) + lor[2,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

rr[2] <- v[2]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lor[c,k] <- d[k] - d[c]
    log(or[c,k]) <- lor[c,k]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.


list(NT=11, NS=19,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: adverse events
```

m.tau= -0.84, sd.tau=1.24)

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3] t[,4] t[,5] na[]

4.5 90 1.5 92 0.5 90 NA NA NA NA 1 2 5 NA NA 3

0.5 111 2.5 111 NA NA NA NA NA NA 1 2 NA NA NA 2

0.5 64 1.5 68 NA NA NA NA NA NA 1 2 NA NA NA 2

1.5 66 0.5 67 NA NA NA NA NA NA 1 3 NA NA NA 2

1 87 1 84 NA NA NA NA NA NA 1 4 NA NA NA 2

1 124 4 129 NA NA NA NA NA NA 1 7 NA NA NA 2

14 1508 9 1501 NA NA NA NA NA NA 2 6 NA NA NA 2

9 694 10 679 NA NA NA NA NA NA 2 7 NA NA NA 2

2 45 3 45 NA NA NA NA NA NA 2 7 NA NA NA 2

17 1277 21 1254 NA NA NA NA NA NA 2 8 NA NA NA 2

1.5 222 0.5 218 NA NA NA NA NA NA 2 9 NA NA NA 2

1 517 11 517 NA NA NA NA NA NA 3 4 NA NA NA 2

22 1588 11 1596 NA NA NA NA NA NA 3 6 NA NA NA 2

0.5 150 4.5 306 0.5 152 NA NA NA NA 3 6 11 NA NA 3

12 868 5 857 NA NA NA NA NA NA 3 7 NA NA NA 2

16 1564 27 1584 NA NA NA NA NA NA 3 8 NA NA NA 2

3 228 3 225 NA NA NA NA NA NA 3 10 NA NA NA 2

9 173 4 176 NA NA NA NA NA NA 3 11 NA NA NA 2

6 336 5 334 NA NA NA NA NA NA 3 11 NA NA NA 2

END

list(

d=c(NA,0,0,0,0,0,0,0,1,2,0), # one for each treatment

sd.sq=1,

mu=c(0,0,3,0,0, 0,2,0,-1,0, 4,0,3,1,0,1,3, 2, 1))

list(

d=c(NA,1,0,2,0,3,0,0,1,2,-2), # one for each treatment

```
sd.sq=0.1,
mu=c(0,2,1,0,-2, 0,3,0,4,0, 2,0,1,3,0,0,1,0,0) )

list(
d=c(NA,0,0,0,0,0,0,0,1,2,2), # one for each treatment
sd.sq=2,
mu=c(0,3,3,0,4, 0,1,0,-2,0, 1,2,0,2,0,-3,1,2, -1) )
```

M.2.6.6 WinBUGS code for inconsistency model for number of patients with major bleeding

```
VTE - inconsistency model - Elective knee MB
==============================
19 trials
11 treaments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
```

```
# trial-specific LOR distributions
       delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
     }
  }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
  }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS

 Data
# DVT
# nt=no. treatments, ns=no. studies
list(nt=11,ns=19, m.tau= -0.84, sd.tau=1.24)

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 4.5 90 1.5 92 0.5 90 NA NA NA NA 1 2 5 NA NA 3
 0.5 111 2.5 111 NA NA NA NA NA NA 1 2 NA NA NA 2
 0.5 64 1.5 68 NA NA NA NA NA NA 1 2 NA NA NA 2
 1.5 66 0.5 67 NA NA NA NA NA NA 1 3 NA NA NA 2
 1 87 1 84 NA NA NA NA NA NA 1 4 NA NA NA 2
 1 124 4 129 NA NA NA NA NA NA 1 7 NA NA NA 2
 14 1508 9 1501 NA NA NA NA NA NA 2 6 NA NA NA 2
 9 694 10 679 NA NA NA NA NA NA 2 7 NA NA NA 2
```

2 45 3 45 NA NA NA NA NA NA 2 7 NA NA NA 2

17 1277 21 1254 NA NA NA NA NA NA 2 8 NA NA NA 2

1.5 222 0.5 218 NA NA NA NA NA NA 2 9 NA NA NA 2

1 517 11 517 NA NA NA NA NA NA 3 4 NA NA NA 2

22 1588 11 1596 NA NA NA NA NA NA 3 6 NA NA NA 2

0.5 150 4.5 306 0.5 152 NA NA NA NA 3 6 11 NA NA 3

12 868 5 857 NA NA NA NA NA NA 3 7 NA NA NA 2

16 1564 27 1584 NA NA NA NA NA NA 3 8 NA NA NA 2

3 228 3 225 NA NA NA NA NA NA 3 10 NA NA NA 2

9 173 4 176 NA NA NA NA NA NA 3 11 NA NA NA 2

6 336 5 334 NA NA NA NA NA NA 3 11 NA NA NA 2

END

INITS

#chain 1

list(sd.sq=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,1,0,-1),

d = structure(.Data = c(

NA,0,0,0,0,0,0,0,0,0,

NA,NA,0,0,0,0,0,0,0,0,

NA,NA,NA,0,0,0,0,0,0,0,

NA,NA,NA,NA,0,0,0,0,0,0,

NA,NA,NA,NA,NA,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,0),

.Dim = c(10,11)))

chain 2

```
list(sd.sq=1.5,  mu=c(2,1,3,1,2,   0,2,0,-1,3,   2,0,1,3,1,   1,2,0,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5 ),
.Dim = c(10,11))  )


# chain 3
list(sd.sq=3,  mu=c(2,0.5,3,0.5,2,   -2,2,1,-1,3,    2,1,1,3,1,     0,1,-1,-3),
d = structure(.Data = c(
        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,3,
        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,3,
        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,3,
        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,3,
        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,3,
        NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,3,
        NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,3,
        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3  ),
.Dim = c(10,11))  )
```

M.3 Network meta-analysis for VTE prophylaxis in those undergoing abdominal surgery

M.3.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in Chapter 35 and forest plots in Appendix L) does not help inform which intervention is most effective as VTE prophylaxis in patients undergoing abdominal surgy. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different treatments; in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial.
- There are frequently multiple overlapping comparisons, which could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions. In this case the outcomes were defined as:

- Deep vein thrombosis (DVT; symptomatic and asymptomatic)
- Pulmonary embolism (PE)
- Major bleeding

The analysis also provided 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.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term “network” better describes the data structure, whereas “mixed treatments” could easily be misinterpreted as referring to combinations of treatments.

M.3.2 Methods

M.3.2.1 Study selection

To estimate the relative risks, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy

combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

M.3.2.2 Outcome measures

The NMA evidence reviews for interventions considered three clinical efficacy outcomes identified from the clinical evidence review; number of people with DVT, number of people with PE and number of people with major bleeding. Other outcomes were not considered for the NMA as they were infrequently reported across the studies. The GDG considered that these outcomes were the most critical clinical outcomes for testing effectiveness of VTE prophylaxis.

M.3.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical evidence review already presented in Chapter 35 of the full guideline and in Appendix H. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in each network are shown in Table 257**.**

Table 257: Treatments included in network meta-analysis

Network 1: Number of people with DVT	**Network 2: Number of people with PE**	**Network 3: Number of people with major bleeding.**
Electrical stimulation	Fondaparinux standard duration	Fondaparinux standard duration
Fondaparinux standard duration	IPCD below knee	No/mechanical prophylaxis
Fondaparinux standard duration + IPCD any location	IPCD full leg	Post-operative LMWH standard duration, standard dose
Foot pump	No prophylaxis	Pre-operative LMWH extended duration, standard dose
IPCD below knee	Post-operative LMWH standard duration, standard dose	Pre-operative LMWH standard duration, high dose
IPCD full leg	Pre-operative LMWH extended duration, standard dose	Pre-operative LMWH standard duration, low dose
IPCD undefined	Pre-operative LMWH standard duration, low dose	Pre-operative LMWH standard duration, standard dose
No prophylaxis	Pre-operative LMWH standard duration, standard dose	UFH standard duration
Post-operative LMWH standard duration, standard dose	AES above knee	-
Post-operative LMWH standard duration, standard dose + IPCD undefined	AES above knee + IPCD full leg	-
Pre-operative LMWH extended duration, standard dose	AES above knee + UFH standard	-
Pre-operative LMWH standard duration, high dose	UFH standard duration	-
Pre-operative LMWH standard duration, low dose	VKA standard duration	-
Pre-operative LMWH standard duration, standard dose	-	-
AES above knee	-	-
AES above knee + IPCD full leg	-	-

AES above knee + UFH standard	-	-
AES below knee	-	-
AES combination + IPCD full leg	-	-
AES undefined	-	-
UFH standard duration	-	-
VKA standard duration	-	-

The details of these interventions can be found in the clinical evidence review in Chapter 35 of the full guideline and evidence tables in Appendix H.

M.3.2.4 Baseline risk

The baseline risk is defined here as the risk of achieving the outcome of interest in the no prophylaxis group. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks.

Baseline odds were derived by the logistic regression in WinBUGS. This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of baseline and relative effects is accounted for in the model. This method produced baseline odds [mean (SD)] as follows:

- -1.372 (1.174) for number of patients with DVT in the no prophylaxis group
- -3.939 (2.201) for number of patients with PE in the no prophylaxis group
- -5.331 (3.482) for the number of patients with major bleeding in the no/mechanical prophylaxis group.

For details of data informing these models, please refer to the full analyses in sections M.3.6.1, M.3.6.4 and M.3.6.6.

M.3.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome subgroup, a diagram of the evidence network is presented in section M.3.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. These were estimated from the baseline models for the dichotomous outcomes using the following equations.

Predictive probability of response (MeanA) =mean of mu.new

Precision (PrecA)=1/(standard deviation of mu.new)^2

A non-informative prior distribution was used to maximise the weighting given to the data for continuous outcomes. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 600,000 simulations were run to produce the outputs. For the baseline analyses, a series of 100,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations

were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 35, and Appendix H).

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:

$$\widetilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$\boldsymbol{p} = \frac{\boldsymbol{e}^{\widetilde{\boldsymbol{\theta}}}}{\mathbf{1} + \boldsymbol{e}^{\widetilde{\boldsymbol{\theta}}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability ($\boldsymbol{p_b}$) to get treatment specific relative risks ($\boldsymbol{rr_b}$):

$$\boldsymbol{p_b} = \frac{\boldsymbol{e}^{\boldsymbol{BO}}}{\mathbf{1} + \boldsymbol{e}^{\boldsymbol{BO}}}$$

$$\boldsymbol{rr_b} = \frac{\boldsymbol{p}}{\boldsymbol{p_b}}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

We also calculated the overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the relative risks from the direct evidence (from pair-wise meta-analysis) to the relative risks from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the relative risk from the NMA did not fit within the confidence interval of the relative risk from the direct comparison. We further

tested for inconsistency by developing inconsistency models for networks of binary outcomes using the TSD 4 template from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). We compared the posterior mean of the residual deviance between the consistency and inconsistency models to see which was a better fit to the data (closest to the number of trial arms in each network) and checked the difference in deviance information criterion (DIC) values between the two models was small (less than 3-5) or if it was larger, that the smaller DIC and hence better fitting model was the consistency model. No inconsistency was identified.

M.3.3 Results

M.3.3.1 Deep vein thrombosis (symptomatic and asymptomatic)

Included studies

66 studies were identified as reporting on DVT outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 48 studies involving 22 treatments were included in the network for DVT (symptomatic and asymptomatic). The network can be seen in **Figure 839** and the trial data for each of the studies included in the NMA are presented in **Table 258**.

Figure 839: Network diagram for DVT

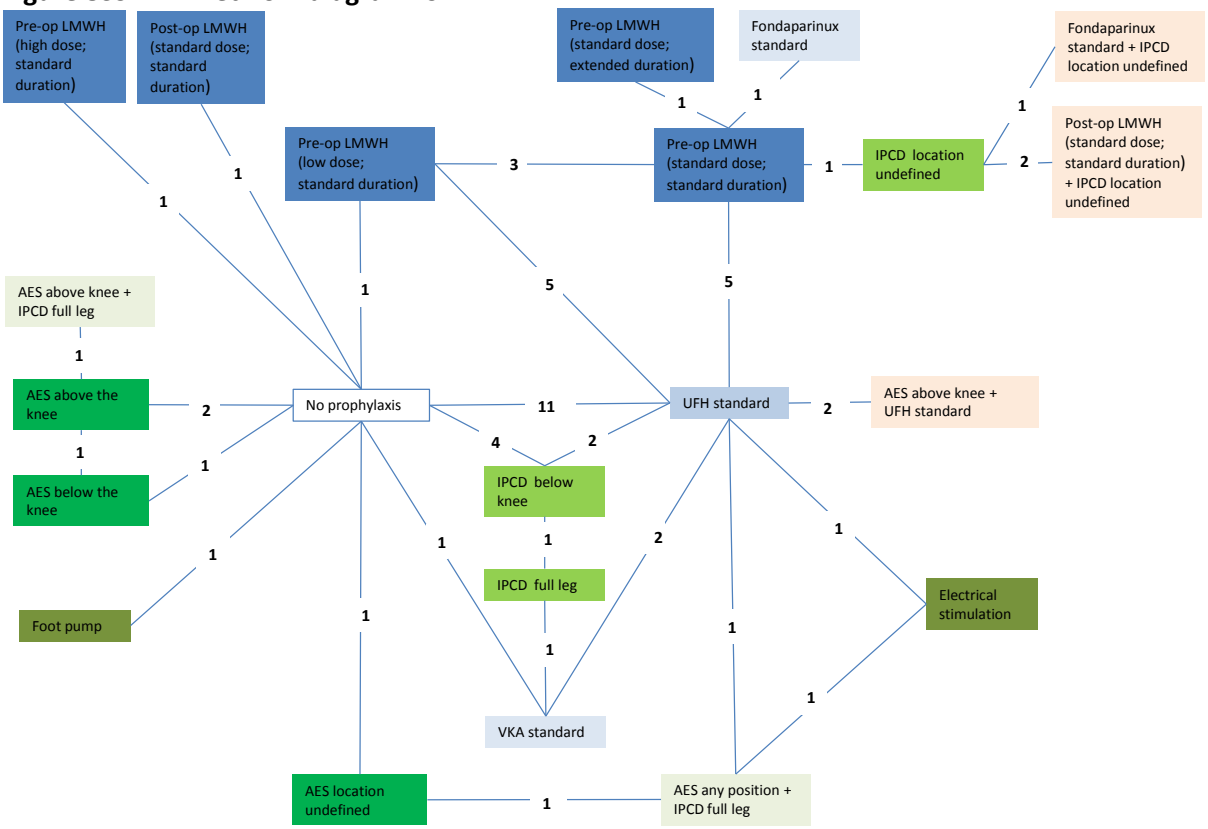


Table 258: Study data for DVT network meta-analysis

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				Events	N	Even	N	Events	N

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
						ts			
Coe 1978	No prophylaxis	UFH standard	IPCD below knee	6	24	6	28	2	29
Tabemer 1978	No prophylaxis	UFH standard	VKA standard	11	48	3	49	3	48
Bergqvist 1980	No prohylaxis	UFH standard	NA	14	51	6	46	NA	NA
Clarke-Pearson 1983	No prohylaxis	UFH standard	NA	11	97	11	88	NA	NA
Gallus 1973	No prohylaxis	UFH standard	NA	4	118	1	108	NA	NA
Gallus 1976	No prohylaxis	UFH standard	NA	12	412	4	408	NA	NA
Gordon-Smith 1972	No prohylaxis	UFH standard	NA	21	50	4	48	NA	NA
Kakkar 1972	No prohylaxis	UFH standard	NA	17	39	3	39	NA	NA
Strand 1925	No prohylaxis	UFH standard	NA	10	50	3	50	NA	NA
Tomgren 1978	No prohylaxis	UFH standard	NA	20	61	10	63	NA	NA
Vandendris 1980	No prohylaxis	UFH standard	NA	13	33	3	31	NA	NA
Buston 1981	No prohylaxis	IPCD below knee	NA	4	57	6	62	NA	NA
Clarke-Pearson 1984A	No prohylaxis	IPCD below knee	NA	11	97	14	97	NA	NA
Clarke-Pearson 1984B	No prohylaxis	IPCD below knee	NA	17	52	5	55	NA	NA
Allan 1983	No prohylaxis	AES position not reported	NA	37	103	15	97	NA	NA
Tsapogas 1971	No prohylaxis	AES below knee	NA	6	44	2	51	NA	NA
Halford 1976	No prohylaxis	AES above knee	NA	23	47	11	48	NA	NA
Turner 1984	No prohylaxis	AES above knee	NA	4.5	93	0.5	105	NA	NA
Scurr 1981	No prohylaxis	Foot pump	NA	15	33	6	33	NA	NA
Marassi 1993	No prohylaxis	Pre-operative LMWH standard high	NA	11	31	2	30	NA	NA
Bergqvist 1996	No prohylaxis	Post-operative LMWH standrd standard	NA	9	41	3	39	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
Ockelford 1989	No prohylaxis	Pre-operative LMWH standard low	NA	14	88	4	95	NA	NA
Clarke-Pearson 1993	UFH standard	IPCD below knee	NA	6	107	3	101	NA	NA
van Vroonhoven 1974	UFH standard	VKA standard	NA	1	50	9	50	NA	NA
Leizorovicz 1991	UFH standard	Pre-operative LMWH standard low	Pre-operative LMWH standard standard	7	429	16	431	7	430
Caen 1988	UFH standard	Pre-operative LMWH standard low	NA	7	190	6	195	NA	NA
Hartl 1990	UFH standard	Pre-operative LMWH standard low	NA	5	115	5	112	NA	NA
Koller 1986B	UFH standard	Pre-operative LMWH standard low	NA	1	72	2	74	NA	NA
Nurmohamed 1995	UFH standard	Pre-operative LMWH standard low	NA	8	709	25	718	NA	NA
Bergqvist 1988	UFH standard	Pre-operative LMWH standard standard	NA	41	497	28	505	NA	NA
Onarheim 1986	UFH standard	Pre-operative LMWH standard standard	NA	0.5	28	1.5	26	NA	NA
Bergqvist 1986	UFH standard	Pre-operative LMWH standard standard	NA	9	217	13	215	NA	NA
Wille-Jorgensen 1991	UFH standard	AES above knee + UFH standard	NA	12	81	2	79	NA	NA
Wille-Jorgensen 1985	UFH standard	AES above knee + UFH standard	NA	7	90	1	86	NA	NA
Nicolaides 1983	UFH standard	Electrical stimulation	AES combination + IPCD full leg	7	50	12	50	3	50
Soderdahl 1997	IPCD below knee	IPCD full leg	NA	1.5	44	0.5	48	NA	NA
Chandhoke 1992	VKA standard	IPCD full leg	NA	0.5	54	2.5	48	NA	NA
Gao 2012	AES position not reported	AES combination + IPCD full leg	NA	14	56	5	52	NA	NA
Porteous 1989	AES below knee	AES above knee	NA	1	58	3	56	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
Caprini 1983	AES above knee	AES above knee + IPCD full leg	NA	5	39	1	38	NA	NA
Harch 1988	Pre-operative LMWH standard low	Pre-operative LMWH standard standard	NA	2.5	17	0.5	20	NA	NA
Bergqvist 1995	Pre-operative LMWH standard low	Pre-operative LMWH standard standard	NA	124	976	65	981	NA	NA
Bergqvist 2002	Pre-operative LMWH standard standard	Pre-operative LMWH extended standard	NA	20	167	8	165	NA	NA
Agnelli 2005	Pre-operative LMWH standard standard	Fondaparinux standard	NA	59	1018	43	1024	NA	NA
Maxwell 2001	Pre-operative LMWH standard standard	IPCD location un-defined	NA	2	105	1	106	NA	NA
Turpie 2007	IPCD location un-defined	Fondaparinux standard + IPCD any location	NA	22	418	7	424	NA	NA
Sakon 2010	IPCD location un-defined	IPCD undefined + Post-operative LMWH standard standard	NA	6	31	1	78	NA	NA
Song 2014	IPCD location un-defined	IPCD undefined + Post-operative LMWH standard standard	NA	3.5	113	0.5	109	NA	NA

NMA results

Table 259 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 259: Risk ratios for DVT (symptomatic and asymptomatic)

Comparisons		Risk ratio	
		Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	UFH standard	0.36 (0.10, 1.27)	0.35 (0.221, 0.62)
	IPCD below knee	0.64 (0.26, 1.59)	0.53 (0.22, 0.95)
	VKA standard	0.27 (0.08, 0.92)	0.58 (0.17, 1.44)
	AES position not reported	0.43 (0.25, 0.73)	0.40 (0.12, 1.07)
	AES below knee	0.29 (0.06, 1.35)	0.18 (0.03, 0.82)
	AES above knee	0.41 (0.23, 0.73)	0.34 (0.10, 0.91)
	Foot pump	0.40 (0.18, 0.90)	0.32 (0.06, 1.20)
	Pre-operative LMWH standard duration, high	0.19 (0.05, 0.78)	0.14 (0.01, 0.83)

		Risk ratio	
	dose		
	Post-operative LMWH standard duration, standard dose	0.35 (0.10, 1.20)	0.34 (0.05, 1.41)
	Pre-operative LMWH standard duration, low dose	0.26 (0.09, 0.77)	0.57 (0.27, 1.01)
	Pre-operative LMWH standard duration, standard dose	-	0.31 (0.13, 0.69)
	AES above knee + UFH standard	-	0.05 (0.01, 0.24)
	Electrical stimulation	-	0.65 (0.15, 2.00)
	AES combination + IPCD full leg	-	0.13 (0.03, 0.54)
	IPCD full leg	-	0.85 (0.10, 3.90)
	AES above knee + IPCD full leg	-	0.05 (0.00, 0.63)
	Pre-operative LMWH extended duration, standard dose	-	0.12 (0.02, 0.60)
	Fondaparinux standard	-	0.23 (0.05, 0.87)
	IPCD location un-defined	-	0.14 (0.00, 1.63)
	Fondaparinux standard + IPCD any location	-	0.04 (0.00, 0.91)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.28)
Versus UFH standard duration	IPCD below knee	0.42 (0.16, 1.15)	1.46 (0.72, 3.01)
	VKA standard	3.03 (1.00, 9.18)	1.57 (0.53, 4.38)
	AES position not reported	-	1.11 (0.34, 3.30)
	AES below knee	-	0.52 (0.08, 2.44)
	AES above knee	-	0.94 (0.27, 2.87)
	Foot pump	-	0.89 (0.17, 3.80)
	Pre-operative LMWH standard duration, high dose	-	0.40 (0.04, 2.43)
	Post-operative LMWH standard duration, standard dose	-	0.93 (0.13, 4.49)
	Pre-operative LMWH standard duration, low dose	1.27 (0.93, 1.73)	1.57 (0.91, 2.76)
	Pre-operative LMWH standard duration, standard dose	0.85 (0.59, 1.24)	0.88 (0.46, 1.63)
	AES above knee + UFH standard	0.16 (0.05, 0.54)	0.14 (0.02, 0.57)
	Electrical stimulation	1.71 (0.74, 3.99)	1.75 (0.46, 6.06)
	AES combination + IPCD full leg	0.43 (0.12, 1.56)	0.38 (0.09, 1.38)
	IPCD full leg	-	2.24 (0.30, 12.75)
	AES above knee + IPCD full leg	-	0.13 (0.00, 1.76)
	Pre-operative LMWH extended duration, standard dose	-	0.34 (0.07, 1.52)
	Fondaparinux standard	-	0.64 (0.16, 2.32)
	IPCD location un-defined	-	0.38 (0.01, 4.66)
	Fondaparinux standard + IPCD any location	-	0.11 (0.00, 2.43)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 0.74)
Versus IPCD below knee	VKA standard	-	1.09 (0.32, 3.45)
	AES position not reported	-	0.76 (0.21, 2.56)

		Risk ratio	
	AES below knee	-	0.36 (0.05, 1.79)
	AES above knee	-	0.65 (0.17, 2.15)
	Foot pump	-	0.61 (0.11, 2.80)
	Pre-operative LMWH standard duration, high dose	-	0.28 (0.02, 1.76)
	Post-operative LMWH standard duration, standard dose	-	0.64 (0.08, 3.27)
	Pre-operative LMWH standard duration, low dose	-	1.07 (0.46, 2.60)
	Pre-operative LMWH standard duration, standard dose	-	0.60 (0.23, 1.52)
	AES above knee + UFH standard	-	0.09 (0.01, 0.47)
	Electrical stimulation	-	1.20 (0.27, 4.83)
	AES combination + IPCD full leg	-	0.26 (0.05, 1.10)
	IPCD full leg	0.31 (0.01, 7.31)	1.54 (0.21, 8.61)
	AES above knee + IPCD full leg	-	0.09 (0.00, 1.28)
	Pre-operative LMWH extended duration, standard dose	-	0.23 (0.04, 1.22)
	Fondaparinux standard	-	0.44 (0.09, 1.88)
	IPCD location un-defined	-	0.26 (0.01, 3.42)
	Fondaparinux standard + IPCD any location	-	0.08 (0.00, 1.78)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.54)
Versus VKA standard duration	AES position not reported	-	0.71 (0.16, 3.10)
	AES below knee	-	0.33 (0.04, 2.08)
	AES above knee	-	0.60 (0.13, 2.64)
	Foot pump	-	0.56 (0.08, 3.25)
	Pre-operative LMWH standard duration, high dose	-	0.26 (0.02, 2.01)
	Post-operative LMWH standard duration, standard dose	-	0.59 (0.07, 3.77)
	Pre-operative LMWH standard duration, low dose	-	0.99 (0.32, 3.34)
	Pre-operative LMWH standard duration, standard dose	-	0.56 (0.17, 1.93)
	AES above knee + UFH standard	-	0.09 (0.01, 0.52)
	Electrical stimulation	-	1.11 (0.21, 5.54)
	AES combination + IPCD full leg	-	0.24 (0.04, 1.25)
	IPCD full leg	0.18 (0.01, 3.60)	1.41 (0.21, 8.02)
	AES above knee + IPCD full leg	-	0.08 (0.00, 1.37)
	Pre-operative LMWH extended duration, standard dose	-	0.22 (0.03, 1.37)
	Fondaparinux standard	-	0.41 (0.07, 2.14)
	IPCD location un-defined	-	0.24 (0.01, 3.62)
	Fondaparinux standard + IPCD any location	-	0.07 (0.00, 1.83)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.56)

		Risk ratio	
Versus AES position not reported	AES below knee	-	0.47 (0.06, 3.03)
	AES above knee	-	0.85 (0.18, 3.87)
	Foot pump	-	0.80 (0.12, 4.79)
	Pre-operative LMWH standard duration, high dose	-	0.36 (0.03, 2.92)
	Post-operative LMWH standard duration, standard dose	-	0.84 (0.10, 5.62)
	Pre-operative LMWH standard duration, low dose	-	1.41 (0.44, 5.16)
	Pre-operative LMWH standard duration, standard dose	-	0.79 (0.22, 2.97)
	AES above knee + UFH standard	-	0.12 (0.02, 0.77)
	Electrical stimulation	-	1.57 (0.33, 7.46)
	AES combination + IPCD full leg	0.38 (0.15, 0.99)	0.34 (0.09, 1.17)
	IPCD full leg	-	2.01 (0.22, 15.68)
	AES above knee + IPCD full leg	-	0.12 (0.00, 1.97)
	Pre-operative LMWH extended duration, standard dose	-	0.31 (0.04, 2.06)
	Fondaparinux standard	-	0.58 (0.10, 3.25)
	IPCD location un-defined	-	0.34 (0.01, 5.60)
	Fondaparinux standard + IPCD any location	-	0.10 (0.00, 2.73)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 0.81)
Versus AES below the knee	AES above knee	3.11 (0.33, 28.99)	1.78 (0.37, 11.60)
	Foot pump	-	1.69 (0.19, 17.66)
	Pre-operative LMWH standard duration, high dose	-	0.78 (0.05, 10.05)
	Post-operative LMWH standard duration, standard dose	-	1.76 (0.16, 19.83)
	Pre-operative LMWH standard duration, low dose	-	3.00 (0.61, 22.24)
	Pre-operative LMWH standard duration, standard dose	-	1.68 (0.31, 12.43)
	AES above knee + UFH standard	-	0.26 (0.02, 2.86)
	Electrical stimulation	-	3.36 (0.45, 32.66)
	AES combination + IPCD full leg	-	0.73 (0.09, 7.04)
	IPCD full leg	-	4.27 (0.36, 54.64)
	AES above knee + IPCD full leg	-	0.26 (0.01, 5.18)
	Pre-operative LMWH extended duration, standard dose	-	0.66 (0.07, 7.38)
	Fondaparinux standard	-	1.23 (0.15, 12.30)
	IPCD location un-defined	-	0.73 (0.02, 17.86)
	Fondaparinux standard + IPCD any location	-	0.22 (0.00, 8.27)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.04 (0.00, 2.35)
Versus AES above the	Foot pump	-	0.94 (0.14, 5.77)
	Pre-operative LMWH standard duration, high	-	0.43 (0.03, 3.56)

		Risk ratio	
knee	dose		
	Post-operative LMWH standard duration, standard dose	-	0.99 (0.12, 6.71)
	Pre-operative LMWH standard duration, low dose	-	1.66 (0.51, 6.36)
	Pre-operative LMWH standard duration, standard dose	-	0.93 (0.26, 3.69)
	AES above knee + UFH standard	-	0.15 (0.02, 0.96)
	Electrical stimulation	-	1.86 (0.34, 10.48)
	AES combination + IPCD full leg	-	0.40 (0.07, 2.30)
	IPCD full leg	-	2.36 (0.26, 19.24)
	AES above knee + IPCD full leg	0.21 (0.03, 1.68)	0.15 (0.00, 1.43)
	Pre-operative LMWH extended duration, standard dose	-	0.36 (0.05, 2.50)
	Fondaparinux standard	-	0.68 (0.11, 4.02)
	IPCD location un-defined	-	0.41 (0.01, 6.71)
	Fondaparinux standard + IPCD any location	-	0.12 (0.00, 3.29)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 0.98)
Versus foot pump	Pre-operative LMWH standard duration, high dose	-	0.46 (0.03, 4.87)
	Post-operative LMWH standard duration, standard dose	-	1.04 (0.10, 9.67)
	Pre-operative LMWH standard duration, low dose	-	1.77 (0.39, 10.02)
	Pre-operative LMWH standard duration, standard dose	-	0.99 (0.20, 5.73)
	AES above knee + UFH standard	-	0.16 (0.02, 1.36)
	Electrical stimulation	-	1.97 (0.28, 15.29)
	AES combination + IPCD full leg	-	0.43 (0.06, 3.34)
	IPCD full leg	-	2.50 (0.23, 26.76)
	AES above knee + IPCD full leg	-	0.15 (0.00, 3.09)
	Pre-operative LMWH extended duration, standard dose	-	0.39 (0.04, 3.56)
	Fondaparinux standard	-	0.73 (0.09, 5.77)
	IPCD location un-defined	-	0.43 (0.01, 8.79)
	Fondaparinux standard + IPCD any location	-	0.13 (0.00, 4.15)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 1.19)
Versus pre-operative LMWH standard duration, high dose	Post-operative LMWH standard duration, standard dose	-	2.28 (0.17, 37.32)
	Pre-operative LMWH standard duration, low dose	-	3.89 (0.61, 44.72)
	Pre-operative LMWH standard duration, standard dose	-	2.17 (0.32, 25.28)
	AES above knee + UFH standard	-	0.34 (0.03, 5.45)
	Electrical stimulation	-	4.36 (0.47, 63.35)

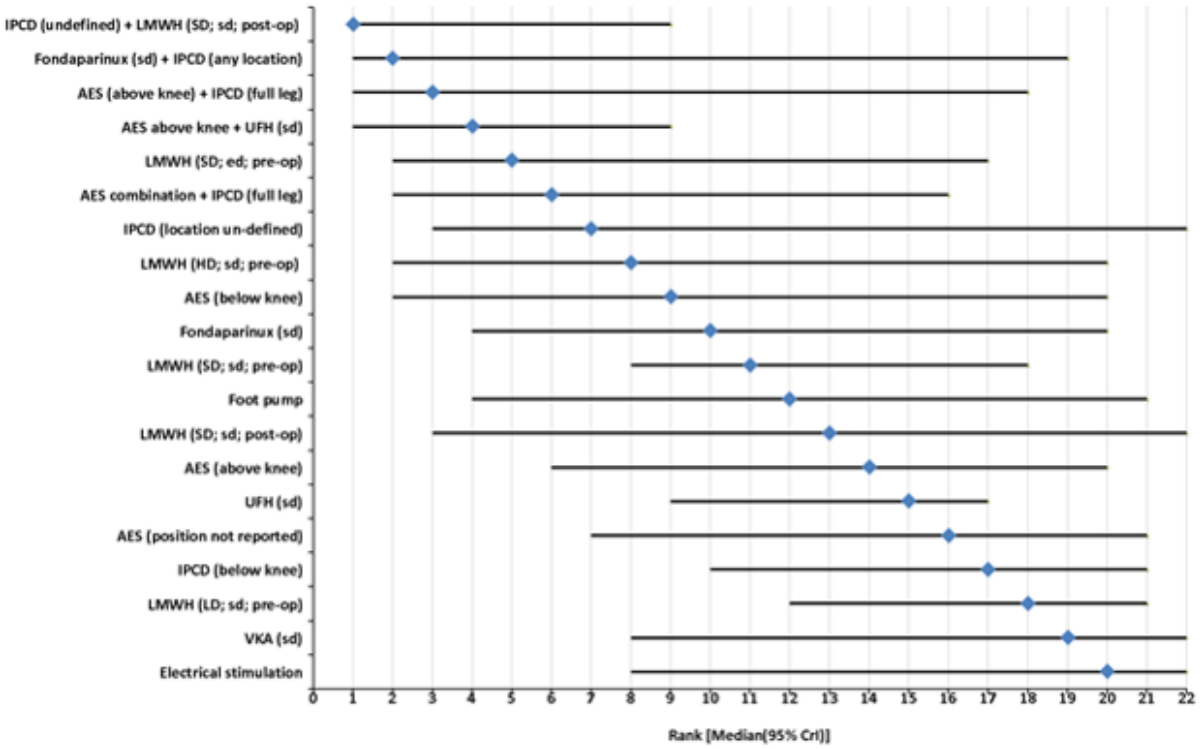
		Risk ratio	
	AES combination + IPCD full leg	-	0.94 (0.09, 13.53)
	IPCD full leg	-	5.54 (0.41, 99.61)
	AES above knee + IPCD full leg	-	0.33 (0.01, 10.68)
	Pre-operative LMWH extended duration, standard dose	-	0.85 (0.07, 13.89)
	Fondaparinux standard	-	1.60 (0.16, 23.52)
	IPCD location un-defined	-	0.95 (0.02, 30.24)
	Fondaparinux standard + IPCD any location	-	0.28 (0.00, 13.34)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.05 (0.00, 3.76)
Versus post-operative LMWH standard duration, standard dose	Pre-operative LMWH standard duration, low dose	-	1.68 (0.33, 12.74)
	Pre-operative LMWH standard duration, standard dose	-	0.94 (0.17, 7.14)
	AES above knee + UFH standard	-	0.15 (0.01, 1.61)
	Electrical stimulation	-	1.88 (0.25, 18.67)
	AES combination + IPCD full leg	-	0.41 (0.05, 4.02)
	IPCD full leg	-	2.41 (0.20, 31.62)
	AES above knee + IPCD full leg	-	0.15 (0.00, 3.45)
	Pre-operative LMWH extended duration, standard dose	-	0.37 (0.04, 4.13)
	Fondaparinux standard	-	0.70 (0.08, 6.91)
	IPCD location un-defined	-	0.42 (0.01, 9.72)
	Fondaparinux standard + IPCD any location	-	0.12 (0.00, 4.59)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 1.28)
Versus pre-operative LMWH standard duration, low dose	Pre-operative LMWH standard duration, standard dose	0.51 (0.39, 0.66)	0.56 (0.28,1.05)
	AES above knee + UFH standard	-	0.09 (0.01, 0.41)
	Electrical stimulation	-	1.13 (0.26, 4.17)
	AES combination + IPCD full leg	-	0.24 (0.05, 0.98)
	IPCD full leg	-	1.44 (0.18, 8.41)
	AES above knee + IPCD full leg	-	0.08 (0.00, 1.19)
	Pre-operative LMWH extended duration, standard dose	-	0.22 (0.04, 0.98)
	Fondaparinux standard	-	0.41 (0.10, 1.48)
	IPCD location un-defined	-	0.24 (0.01, 2.94)
	Fondaparinux standard + IPCD any location	-	0.07 (0.00, 1.54)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.48)
Versus pre-operative LMWH standard duration, standard dose	AES above knee + UFH standard	-	0.16 (0.02, 0.74)
	Electrical stimulation	-	1.99 (0.46, 8.11)
	AES combination + IPCD full leg	-	0.43 (0.09, 1.82)
	IPCD full leg	-	2.54 (0.32, 16.59)
	AES above knee + IPCD full leg	-	0.15 (0.00, 2.19)
	Pre-operative LMWH extended duration,	0.40 (0.18, 0.89)	0.39 (0.09, 1.51)

		Risk ratio	
	standard dose		
	Fondaparinux standard	0.72 (0.49, 1.06)	0.73 (0.21, 2.28)
	IPCD location un-defined	0.50 (0.05, 5.38)	0.44 (0.01, 5.03)
	Fondaparinux standard + IPCD any location	-	0.13 (0.00, 2.58)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 0.79)
Versus AES above knee + UFH standard duration	Electrical stimulation	-	12.82 (1.83, 112.70)
	AES combination + IPCD full leg	-	2.76 (0.37, 24.75)
	IPCD full leg	-	16.32 (1.43, 199.70)
	AES above knee + IPCD full leg	-	0.96 (0.02, 23.31)
	Pre-operative LMWH extended duration, standard dose	-	2.49 (0.29, 24.71)
	Fondaparinux standard	-	4.65 (0.65, 42.46)
	IPCD location un-defined	-	2.76 (0.06, 62.80)
	Fondaparinux standard + IPCD any location	-	0.83 (0.01, 28.66)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.16 (0.00, 8.15)
Versus electrical stimulation	AES combination + IPCD full leg	-	0.22 (0.04, 0.93)
	IPCD full leg	-	1.28 (0.13, 10.84)
	AES above knee + IPCD full leg	-	0.08 (0.00, 1.38)
	Pre-operative LMWH extended duration, standard dose	-	0.20 (0.02, 1.40)
	Fondaparinux standard	-	0.37 (0.06, 2.30)
	IPCD location un-defined	-	0.22 (0.01, 3.67)
	Fondaparinux standard + IPCD any location	-	0.06 (0.00, 1.83)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.55)
Versus AES combination + IPCD full leg	IPCD full leg	-	5.85 (0.58, 56.54)
	AES above knee + IPCD full leg	-	0.35 (0.01, 6.88)
	Pre-operative LMWH extended duration, standard dose	-	0.90 (0.11, 7.21)
	Fondaparinux standard	-	1.69 (0.25, 11.55)
	IPCD location un-defined	-	1.00 (0.02, 19.07)
	Fondaparinux standard + IPCD any location	-	0.30 (0.01, 9.04)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.06 (0.00, 2.57)
Versus IPCD full leg	AES above knee + IPCD full leg	-	0.06 (0.00, 1.48)
	Pre-operative LMWH extended duration, standard dose	-	0.15 (0.01, 1.83)
	Fondaparinux standard	-	0.29 (0.03, 2.98)
	IPCD location un-defined	-	0.17 (0.00, 4.22)
	Fondaparinux standard + IPCD any location	-	0.05 (0.00, 1.96)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.56)
Versus AES	Pre-operative LMWH extended duration,	-	2.61 (0.12, 143.30)

		Risk ratio	
above the knee + IPCD full leg	standard dose		
	Fondaparinux standard	-	4.88 (0.25, 260.40)
	IPCD location un-defined	-	2.85 (0.04, 266.80)
	Fondaparinux standard + IPCD any location	-	0.87 (0.01, 106.20)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.17 (0.00, 28.67)
Versus pre-operative LMWH extended duration, standard dose	Fondaparinux standard	-	1.88 (0.30, 12.20)
	IPCD location un-defined	-	1.11 (0.03, 19.99)
	Fondaparinux standard + IPCD any location	-	0.33 (0.01, 9.53)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.06 (0.00, 2.69)
Versus fondaparinux standard duration	IPCD location un-defined	-	0.60 (0.02, 9.40)
	Fondaparinux standard + IPCD any location	-	0.18 (0.00, 4.57)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.03 (0.00, 1.31)
Versus IPCD location un-defined	Fondaparinux standard + IPCD any location	0.31 (0.14, 0.73)	0.31 (0.07, 1.23)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	0.09 (0.02, 0.46)	0.06 (0.00, 0.42)
Versus fondaparinux standard duration + IPCD any location	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.20 (0.01, 2.17)

Figure 840 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 22 different interventions being evaluated in comparison with no prophylaxis.

Figure 840: Rank order for interventions based the relative risk of experiencing DVT compared to baseline (no prophylaxis)



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 101 reported. This corresponds fairly well to the total number of trial arms, 100. The between trial standard deviation in the random effects analysis was 0.57 (95% CI 0.23 to 0.96). On evaluating inconsistency by comparing risk ratios, the NMA estimated risk ratio for IPCD below the knee compared to UFH at a standard duration (1.46 [0.72, 3.01]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.42 [0.16, 1.15]). An inconsistency model was run and the DIC statistics were as follows in **Table 260**. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 260: DIC for DVT (symptomatic and asymptomatic) – random effects

	DIC	TotResDev
Consistency model	530.880	101
Inconsistency model	532.606	100

M.3.3.2 Pulmonary embolism (PE)

Included studies

51 studies were identified as reporting on PE outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other

intervention in the network, 26 studies involving 13 treatments were included in the network for PE. The network can be seen in **Figure 841** and the trial data for each of the studies included in the NMA are presented in **Table 261**.

Figure 841: Network diagram for PE

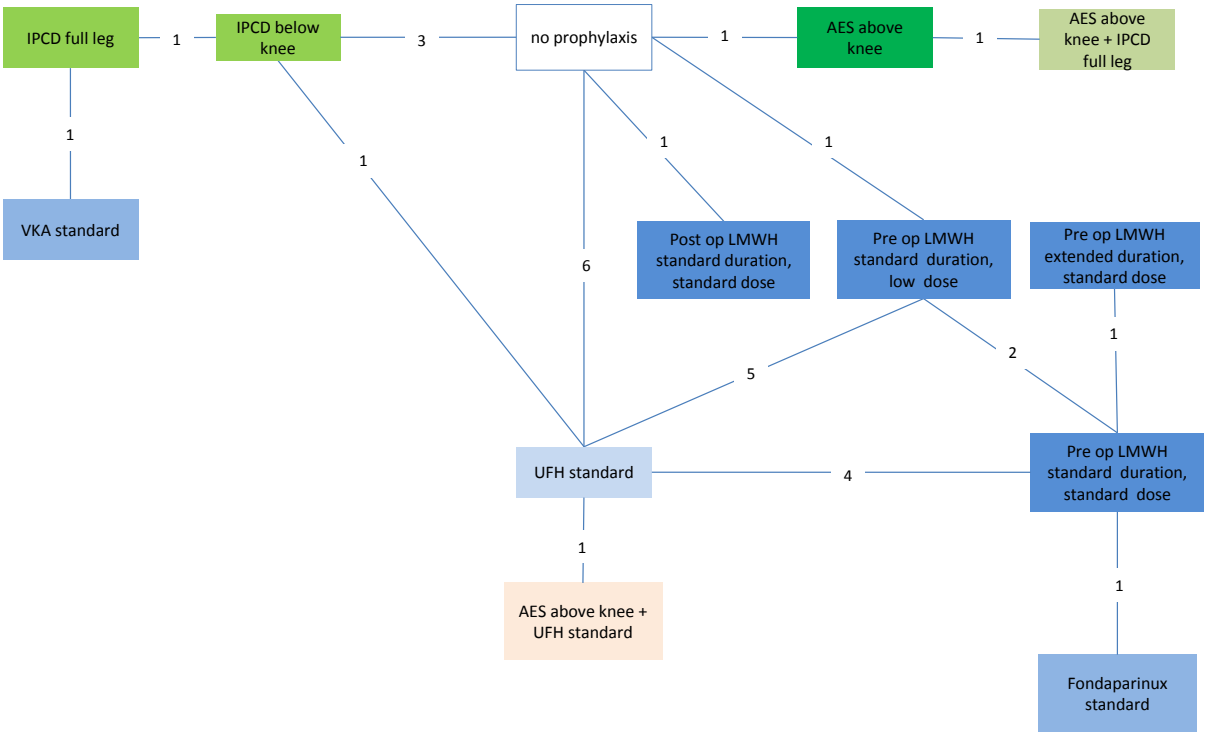


Table 261: Study data for PE network meta-analysis

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				Events	N	Events	N	Events	N
Clarke-Pearson 1984A	no prophylaxis	IPCD below knee	NA	1	97	4	97	NA	NA
Clarke-Pearson 1984B	no prophylaxis	IPCD below knee	NA	1	52	2	55	NA	NA
Coe 1978	no prophylaxis	IPCD below knee	UFH standard	1	24	1	29	1	28
Gordon-Smith 1972	no prophylaxis	UFH standard	NA	0.5	51	2.5	49	NA	NA
Bejjani 1983	no prophylaxis	UFH standard	NA	1.5	18	0.5	18	NA	NA
Clarke-Pearson 1983	no prophylaxis	UFH standard	NA	0.5	98	4.5	89	NA	NA
Lahnborg 1975 + 1974	no prophylaxis	UFH standard	NA	24	54	9	58	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
Tongren 1978	no prophylaxis	UFH standard	NA	2	61	1	63	NA	NA
Bergqvist 1996	no prophylaxis	Post op LMWH standard standard	NA	1.5	42	0.5	40	NA	NA
Ockelford 1989	no prophylaxis	Pre op LMWH standard low	NA	2.5	89	0.5	96	NA	NA
Holford 1976	no prophylaxis	AES above knee	NA	1.5	48	0.5	49	NA	NA
Soderdahl 1997	IPCD below knee	IPCD full leg	NA	0.5	44	1.5	48	NA	NA
Borstad 1992	UFH standard	Pre op LMWH standard low	NA	0.5	71	1.5	72	NA	NA
Caen 1988	UFH standard	Pre op LMWH standard low	NA	1.5	191	0.5	196	NA	NA
Kakkar 1993	UFH standard	Pre op LMWH standard low	NA	11	1915	8	1894	NA	NA
Koller 1986	UFH standard	Pre op LMWH standard low	NA	1.5	73	0.5	75	NA	NA
Leizorovicz 1991	UFH standard	Pre op LMWH standard low	Pre op LMWH standard standard	2	429	4	431	1	430
Wille-Jorgensen 1985	UFH standard	AES above knee + UFH standard	NA	6	90	2	86	NA	NA
Bergqvist 1988	UFH standard	Pre op LMWH standard standard	NA	4.5	498	0.5	506	NA	NA
Fricker 1988	UFH standard	Pre op LMWH standard standard	NA	5.5	41	0.5	41	NA	NA
McLeod 2001	UFH standard	Pre op LMWH standard standard	NA	0.5	469	1.5	469	NA	NA
Bergqvist 1995	Pre op LMWH standard low	Pre op LMWH standard standard	NA	4	976	6	981	NA	NA
Caprini 1983	AES above knee	AES above knee + IPCD full leg	NA	1	39	1	38	NA	NA
Chandhoke 1992	IPCD full leg	VKA standard	NA	1.5	48	0.5	54	NA	NA
Bergqvist 2002	Pre op LMWH standard standard	Pre op LMWH extended standard	NA	2.5	168	0.5	166	NA	NA
Agnelli 2005	Pre op LMWH standard standard	Fondaparinux standard	NA	0.5	1463	2.5	1466	NA	NA

NMA results

Table 262 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 262: Risk ratios for PE

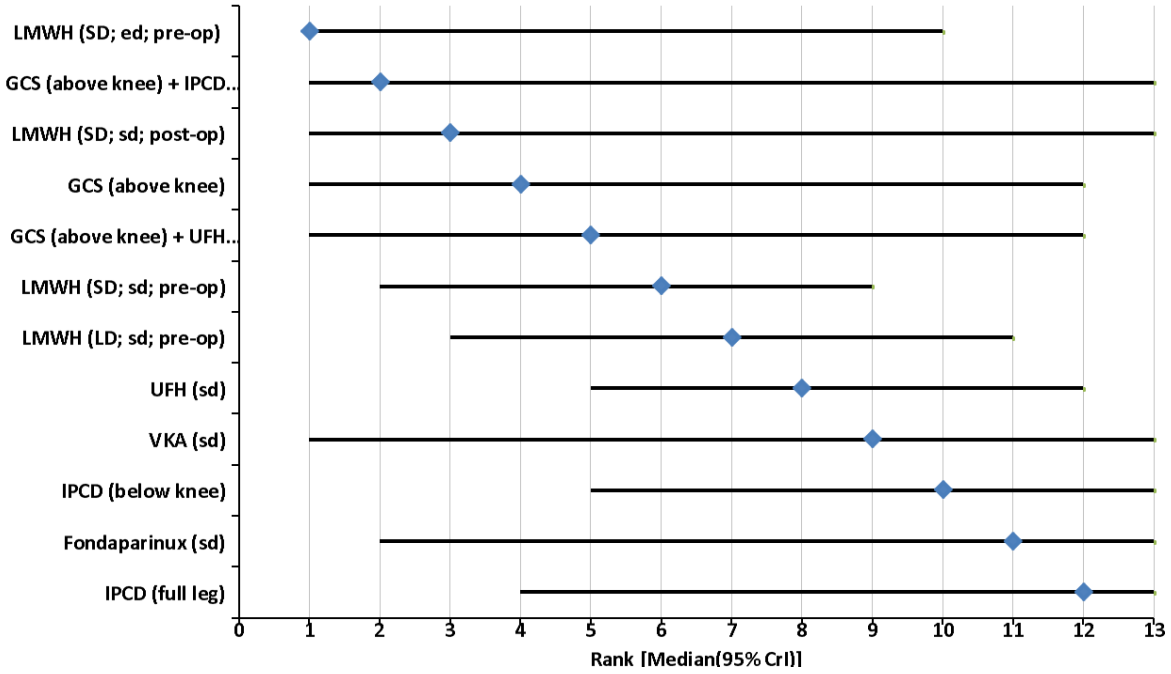
Comparisons		Risk ratio	
		Direct (mean with 95% confidence interval)	**NMA (median with 95% credible interval)**
Versus no prophylaxis	IPCD below the knee	2.19 (0.58, 8.24)	1.87 (0.34, 11.08)
	UFH standard duration	0.60 (0.36, (1.02)	0.81 (0.26, 2.75)
	Post-operative LMWH standard duration, standard dose	0.35 (0.01, 8.34)	0.20 (0.00, 8.38)
	Pre-operative LMWH standard duration, low dose	0.19 (0.01, 3.81)	0.50 (0.10, 2.32)
	AES above the knee	0.33 (0.01, 7.82)	0.20 (0.00, 8.23)
	IPCD full leg	-	5.32 (0.12, 238.70)
	AES above knee + UFH standard duration	-	0.24 (0.01, 4.41)
	Pre-operative LMWH standard duration, standard dose	-	0.29 (0.04, 1.70)
	AES above the knee + IPCD full leg	-	0.19 (0.00, 27.36)
	VKA standard duration	-	1.40 (0.00, 160.60)
	Pre-operative LMWH extended duration, standard dose	-	0.03 (0.00, 1.84)
	Fondaparinux standard duration	-	2.20 (0.04, 136.90)
Versus IPCD below the knee	UFH standard duration	1.04 (0.06, 17.00)	0.43 (0.06, 3.17)
	Post-operative LMWH standard duration, standard dose	-	0.10 (0.00, 6.18)
	Pre-operative LMWH standard duration, low dose	-	0.26 (0.03, 2.39)
	AES above the knee	-	0.10 (0.00, 6.02)
	IPCD full leg	2.75 (0.12, 65.76)	2.61 (0.09, 113.50)
	AES above knee + UFH standard duration	-	0.13 (0.00, 3.39)
	Pre-operative LMWH standard duration, standard dose	-	0.15 (0.01, 1.63)
	AES above the knee + IPCD full leg	-	0.10 (0.00, 18.30)
	VKA standard duration	-	0.81 (0.00, 74.14)
	Pre-operative LMWH extended duration, standard dose	-	0.01 (0.00, 1.31)
	Fondaparinux standard duration	-	1.21 (0.01, 93.75)
Versus UFH standard duration	Post-operative LMWH standard duration, standard dose	-	0.24 (0.00, 12.32)
	Pre-operative LMWH standard duration, low dose	0.88 (0.44, 1.78)	0.62 (0.17, 1.88)

		Risk ratio	
	AES above the knee	-	0.24 (0.00, 12.26)
	IPCD full leg	-	6.53 (0.13, 348.10)
	AES above knee + UFH standard duration	0.35 (0.07, 1.68)	0.31 (0.01, 3.98)
	Pre-operative LMWH standard duration, standard dose	0.24 (0.06, 0.93)	0.37 (0.07, 1.35)
	AES above the knee + IPCD full leg	-	0.24 (0.00, 39.87)
	VKA standard duration	-	1.66 (0.00, 226.70)
	Pre-operative LMWH extended duration, standard dose	-	0.04 (0.00, 1.85)
	Fondaparinux standard duration	-	2.63 (0.05, 167.50)
Versus post-operative LMWH standard duration, standard dose	Pre-operative LMWH standard duration, low dose	-	2.59 (0.04, 2169.00)
	AES above the knee	-	1.01 (0.00, 1859.00)
	IPCD full leg	-	30.87 (0.14, 52120.00)
	AES above knee + UFH standard duration	-	1.31 (0.01, 1562.00)
	Pre-operative LMWH standard duration, standard dose	-	1.54 (0.02, 1365.00)
	AES above the knee + IPCD full leg	-	1.06 (0.00, 3598.00)
	VKA standard duration	-	6.91 (0.00, 20470.00)
	Pre-operative LMWH extended duration, standard dose	-	0.16 (0.00, 316.50)
	Fondaparinux standard duration	-	12.75 (0.04, 23960.00)
Versus pre-operative LMWH standard duration, low dose	AES above the knee	-	0.40 (0.00, 24.51)
	IPCD full leg	-	10.89 (0.19, 678.30)
	AES above knee + UFH standard duration	-	0.50 (0.02, 9.11)
	Pre-operative LMWH standard duration, standard dose	0.87 (0.32, 2.40)	0.60 (0.12, 2.60)
	AES above the knee + IPCD full leg	-	0.39 (0.00, 77.56)
	VKA standard duration	-	2.60 (0.00, 435.90)
	Pre-operative LMWH extended duration, standard dose	-	0.06 (0.00, 3.30)
	Fondaparinux standard duration	-	4.27 (0.09, 313.00)
Versus AES above the knee	IPCD full leg	-	31.09 (0.14, 43070.00)
	AES above knee + UFH standard duration	-	1.28 (0.01, 1369.00)
	Pre-operative LMWH standard duration, standard dose	-	1.49 (0.02, 1131.00)
	AES above the knee + IPCD full leg	1.03 (0.07, 15.82)	1.05 (0.02. 45.55)

		Risk ratio	
	VKA standard duration	-	6.81 (0.00, 18380.00)
	Pre-operative LMWH extended duration, standard dose	-	0.16 (0.00, 279.10)
	Fondaparinux standard duration	-	12.43 (0.05, 21680.00)
Versus IPCD full leg	AES above knee + UFH standard duration	-	0.04 (0.00, 4.81)
	Pre-operative LMWH standard duration, standard dose	-	0.05 (0.00, 3.41)
	AES above the knee + IPCD full leg	-	0.03 (0.00, 16.57)
	VKA standard duration	0.30 (0.01, 7.10)	0.30 (0.00, 4.49)
	Pre-operative LMWH extended duration, standard dose	-	0.00 (0.00, 1.35)
	Fondaparinux standard duration	-	0.50 (0.00, 101.50)
Versus AES above the knee + UFH standard duration	Pre-operative LMWH standard duration, standard dose	-	1.20 (0.06, 31.58)
	AES above the knee + IPCD full leg	-	0.78 (0.00, 316.10)
	VKA standard duration	-	5.00 (0.00, 1871.00)
	Pre-operative LMWH extended duration, standard dose	-	0.12 (0.00, 17.72)
	Fondaparinux standard duration	-	8.99 (0.09, 1518.00)
Versus pre-operative LMWH standard duration, standard dose	AES above the knee + IPCD full leg	-	0.65 (0.00, 147.90)
	VKA standard duration	-	4.32 (0.00, 830.30)
	Pre-operative LMWH extended duration, standard dose	0.20 (0.01, 4.18)	0.11 (0.00, 4.23)
	Fondaparinux standard duration	4.99 (0.24, 103.84)	6.99 (0.22, 484.90)
Versus AES above the knee + IPCD full leg	VKA standard duration	-	6.39 (0.00, 46310.00)
	Pre-operative LMWH extended duration, standard dose	-	0.15 (0.00, 724.50)
	Fondaparinux standard duration	-	12.24 (0.02, 57240.00)
Versus VKA standard duration	Pre-operative LMWH extended duration, standard dose	-	0.02 (0.00, 121.10)
	Fondaparinux standard duration	-	1.55 (0.00, 9161.00)
Versus pre-operative LMWH extended duration, standard dose	Fondaparinux standard duration	-	80.07 (0.41, 134600.00)

Figure 842 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 13 different interventions being evaluated.

Figure 842: Rank order for interventions based the relative risk of experiencing PE compared to baseline (no prophylaxis)



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 55 reported. This corresponds well to the total number of trial arms, 54. The between trial standard deviation in the random effects analysis was 1.01 (95% CI 0.30 to 2.11). No inconsistency was identified between the direct RR and NMA results. An inconsistency model was run and the DIC statistics were as follows in **Table 263**. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 263: DIC for PE – random effects

	DIC	TotResDev
Consistency model	224.072	55
Inconsistency model	225.681	56

M.3.3.3 Major bleeding

Included studies

33 studies were identified as reporting on major bleeding outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any

other intervention in the network, 29 studies involving 8 treatments were included in the network for major bleeding. The network can be seen in **Figure 843** and the trial data for each of the studies included in the NMA are presented in **Table 264**.

Figure 843: Network diagram for major bleeding

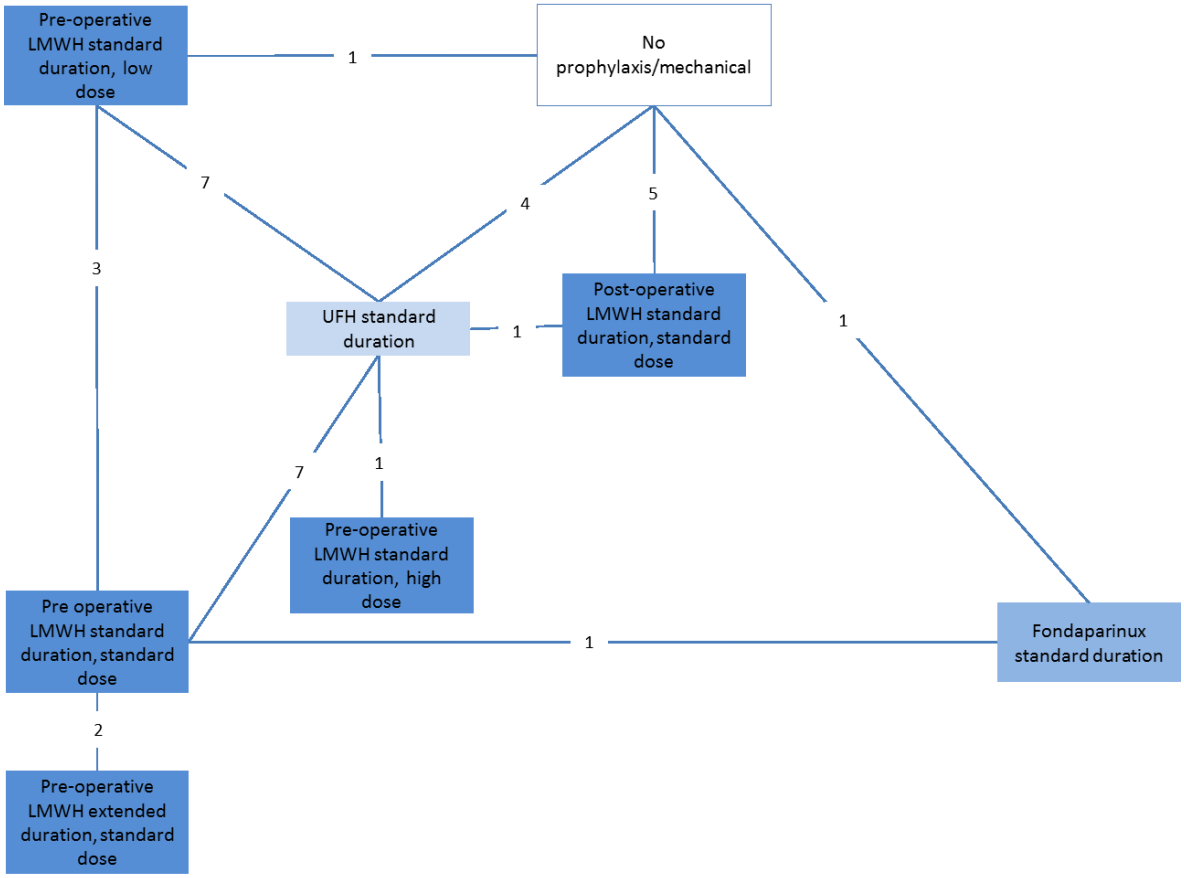


Table 264: Study data for major bleeding network meta-analysis

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				Events	N	Events	N	Events	N
Ockelford 1989	no prophylaxis/mechanical	pre op LMWH standard duration, low dose	NA	4	88	4	95	NA	NA
Osman 2007	no prophylaxis/mechanical	UFH standard duration	Post op LMWH standard duration, standard dose	0	25	0	25	1	25
Allen 1978	no prophylaxis/mechanical	UFH standard duration	NA	0	30	6	30	NA	NA
Bejjani 1983	no prophylaxis/mechanical	UFH standard duration	NA	0	17	1	17	NA	NA
Tongren 1978	no prophylaxis/mechanical	UFH standard duration	NA	23	61	24	63	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
Bergqvist 1996	no prophylaxis/mechanical	Post op LMWH standard duration, standard dose	NA	0	41	1	39	NA	NA
Nagata 2015	no prophylaxis/mechanical	Post op LMWH standard duration, standard dose	NA	1	14	2	16	NA	NA
Sakon 2010	no prophylaxis/mechanical	Post op LMWH standard duration, standard dose	NA	1	38	5	109	NA	NA
Song 2014	no prophylaxis/mechanical	Post op LMWH standard duration, standard dose	NA	0	112	2	108	NA	NA
Turpie 2007	no prophylaxis/mechanical	Fondaparinux standard duration	NA	1	650	10	635	NA	NA
Borstad 1992	pre op LMWH standard duration, low dose	UFH standard duration	NA	14	71	9	70	NA	NA
Kaaja 1992	pre op LMWH standard duration, low dose	UFH standard duration	NA	0	37	6	31	NA	NA
Kakkar 1993	pre op LMWH standard duration, low dose	UFH standard duration	NA	69	1894	91	1915	NA	NA
Koller 1986B	pre op LMWH standard duration, low dose	UFH standard duration	NA	17	74	23	72	NA	NA
Leizorovicz 1991	pre op LMWH standard duration, low dose	UFH standard duration	pre op LMWH standard duration, standard dose	14	431	12	429	10	430
Hartl 1990	pre op LMWH standard duration, low dose	UFH standard duration	NA	2	112	15	115	NA	NA
Nurmohamed 1995	pre op LMWH standard duration, low dose	UFH standard duration	NA	11	725	18	719	NA	NA
Bergqvist 1995	pre op LMWH standard duration, low dose	pre op LMWH standard duration, standard dose	NA	3	1034	13	1036	NA	NA
Hauch 1988	pre op LMWH standard duration, low dose	pre op LMWH standard duration, standard dose	NA	0	16	1	19	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
Bergqvist 1986	UFH standard duration	pre op LMWH standard duration, standard dose	NA	2	217	10	215	NA	NA
Borstad 1988	UFH standard duration	pre op LMWH standard duration, standard dose	NA	13	110	32	105	NA	NA
Fricker 1988	UFH standard duration	pre op LMWH standard duration, standard dose	NA	1	40	2	40	NA	NA
Gonzalez 1996	UFH standard duration	pre op LMWH standard duration, standard dose	NA	5	82	0	84	NA	NA
McLeod 2001	UFH standard duration	pre op LMWH standard duration, standard dose	NA	10	643	18	653	NA	NA
Onarheim 1986	UFH standard duration	pre op LMWH standard duration, standard dose	NA	1	27	1	25	NA	NA
Koller 1986 A	UFH standard duration	pre op LMWH standard duration, high dose	NA	1	20	6	23	NA	NA
Agnelli 2005	Fondaparinux standard duration	pre op LMWH standard duration, standard dose	NA	49	1433	34	1425	NA	NA
Bergqvist 2002	pre op LMWH standard duration, standard dose	pre op LMWH extended duration, standard dose	NA	1	248	3	253	NA	NA
Rasmussen 2006	pre op LMWH standard duration, standard dose	pre op LMWH extended duration, standard dose	NA	4	222	1	205	NA	NA

NMA results

Table 265 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 265: Risk ratios for major bleeding

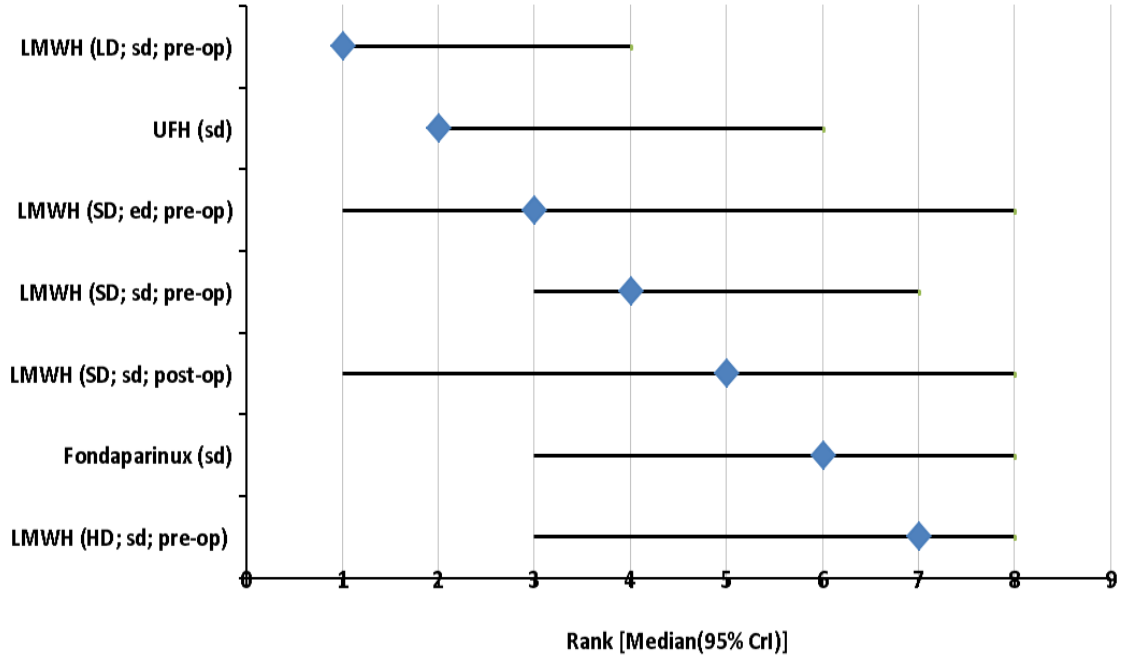
Comparisons		Risk ratio	
		Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis (or mechanical prophylaxis)	Pre-operative LMWH standard duration, low dose	0.93 (0.24, 3.59)	1.21 (0.41, 3.95)
	UFH standard duration	1.30 (0.84, 2.00)	2.01 (0.81, 6.52)
	Post-operative LMWH standard duration, standard dose	2.49 (0.78, 7.91)	2.98 (0.88, 14.80)

		Risk ratio	
	Fondaparinux standard duration	10.24 (1.31, 79.73)	4.98 (1.05, 31.16)
	Pre-operative LMWH standard duration, standard dose	-	2.96 (1.00, 11.16)
	Pre-operative LMWH standard duration, high dose	-	11.26 (1.02, 349.30)
	Pre-operative LMWH extended duration, standard dose	-	2.39 (0.32, 22.51)
Versus pre-operative LMWH standard duration, low dose	UFH standard duration	1.36 (0.9, 2.05)	1.64 (0.94, 3.53)
	Post-operative LMWH standard duration, standard dose	-	2.35 (0.50, 16.10)
	Fondaparinux standard duration	-	4.01 (1.00, 24.20)
	Pre-operative LMWH standard duration, standard dose	1.73 (0.42, 7.19)	2.41 (1.02, 6.33)
	Pre-operative LMWH standard duration, high dose	-	8.95 (0.99, 265.00)
	Pre-operative LMWH extended duration, standard dose	-	1.92 (0.29, 15.24)
Versus UFH standard duration	Post-operative LMWH standard duration, standard dose	0.33 (0.01, 7.81)	1.40 (0.31, 8.28)
	Fondaparinux standard duration	-	2.36 (0.62, 12.34)
	Pre-operative LMWH standard duration, standard dose	1.67 (1.17, 2.39)	1.43 (0.74, 3.04)
	Pre-operative LMWH standard duration, high dose	5.22 (0.68, 39.74)	5.17 (0.64, 138.20)
	Pre-operative LMWH extended duration, standard dose	-	1.18 (0.17, 7.89)
Versus post-operative LMWH standard duration, standard dose	Fondaparinux standard duration	-	1.50 (0.24, 13.47)
	Pre-operative LMWH standard duration, standard dose	-	0.99 (0.17, 5.35)
	Pre-operative LMWH standard duration, high dose	-	3.32 (0.26, 122.30)
	Pre-operative LMWH extended duration, standard dose	-	0.89 (0.07, 8.93)
Versus fondaparinux standard duration	Pre-operative LMWH standard duration, standard dose	0.70 (0.45, 1.07)	0.63 (0.13, 2.18)
	Pre-operative LMWH standard duration, high dose	-	1.96 (0.16, 65.24)
	Pre-operative LMWH extended duration, standard dose	-	0.55 (0.05, 4.00)
Versus pre-operative LMWH standard duration, standard dose	Pre-operative LMWH standard duration, high dose	-	3.46 (0.39, 97.05)
	Pre-operative LMWH extended duration, standard dose	0.83 (0.22, 3.12)	0.90 (0.13, 4.66)
Versus pre-operative LMWH standard duration, high	Pre-operative LMWH extended duration, standard dose	-	0.25 (0.01, 3.49)

		Risk ratio	
dose			

Figure 844 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 8 different interventions being evaluated.

Figure 844: Rank order for interventions based the relative risk of major bleeding compared to baseline (no prophylaxis/mechanical prophylaxis)



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration

Goodness of fit and inconsistency

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 59 reported. This corresponds fairly well to the total number of trial arms, 60. The between trial standard deviation in the random effects analysis was 0.82 (95% CI 0.40 to 1.44). On evaluating inconsistency by comparing risk ratios, the NMA estimated risk ratio for UFH at a standard duration compared to no prophylaxis (2.01 [0.81, 6.52]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (1.30 [0.84, 2.00]). Therefore an inconsistency model was run and the DIC statistics were as follows in Table 266. The difference in the DIC is small (<3-5) which suggests that there is no obvious inconsistency in the network.

Table 266: DIC for major bleeding – random effects

	DIC	TotResDev
Consistency model	299.227	59
Inconsistency model	302.084	60

M.3.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 35 and Appendix H, deciding upon the most clinical and cost effective prophylaxis intervention in patients undergoing abdominal surgery is challenging. In order to overcome the difficulty of interpreting the conclusions from numerous separate comparisons, network meta-analysis of the direct evidence was performed. The findings of the NMA were used to facilitate the guideline committee in decision-making when developing recommendations.

Our analyses were divided into three critical outcomes. 48 studies informed the DVT network where 22 different individual or combination treatments were evaluated including 10 mechanical interventions, eight pharmacological interventions, and three interventions that combined both mechanical and pharmacological prophylaxis. 26 studies informed the PE network of 13 different treatments, including four mechanical interventions, seven pharmacological interventions, and one intervention that combined both mechanical and pharmacological prophylaxis. The major bleeding network included 29 studies evaluating eight treatments, seven of which were pharmacological as for this outcome any mechanical prophylaxis measures were combined with the no prophylaxis intervention as it is believed that mechanical prophylaxis has no associated bleeding risk.

In the DVT network, the three interventions that represented a combination of mechanical and pharmacological prophylaxis featured in the top four best ranked treatments. IPCD (undefined location) plus post-operative LMWH at a standard duration and standard dose was ranked first, IPCD (any location) plus fondaparinux for a standard duration was ranked second, and AES above the knee plus unfractionated heparin for a standard duration was ranked fourth. The treatment in the third spot was a combination of two forms of mechanical prophylaxis (AES above the knee plus IPCD full leg). There is considerable uncertainty about these estimates as the credible intervals are quite wide (with the top intervention spanning nine ranking positions, and the second and third spanning 19 and 18 respectively).

In the PE network the only combination intervention evaluated (AES above the knee plus unfractionated heparin standard duration) came in fifth, and was outranked by pre-operative LMWH extended duration and standard dose, AES above the knee plus IPCD full leg, post-operative LMWH standard duration and standard dose, and AES above the knee alone. However the credible intervals were very wide, with the top ranked treatment spanning 10 rankings, the second and third treatments spanning all 13 rankings, and the fourth and fifth treatments spanning 12 rankings.

In the major bleeding network the highest ranked intervention was the low dose of pre-operative LMWH for a standard duration (with a credible interval spanning four ranking positions). This was followed by unfractionated heparin for a standard duration, then the three standard doses of LMWH preoperatively for either an extended or standard duration, or post-operatively for a standard duration. Fondaparinux for a standard duration came in seventh, and last was the high dose of pre-operative LMWH for a standard duration.

In summary, the three outcomes chosen for analyses were considered to be among the most critical for assessing clinical effectiveness of different VTE prophylaxis strategies. All three networks seemed to fit well, as demonstrated by residual deviance and no obvious inconsistency found in the networks. However the credible intervals around the ranking of treatments in all three networks were wide suggesting considerable uncertainty about these results.

M.3.5 Conclusion

This analysis allowed us to combine findings from many different comparisons presented in the review even when direct comparative data was lacking.

Overall the guideline committee agreed that the results for the three networks were not conclusive. It was acknowledged that a combination of mechanical and pharmacological prophylaxis were likely to be the most effective prophylaxis and therefore may be appropriate to offer those people undergoing abdominal surgery who have been assessed as having a low risk of bleeding. For details of the rationale and discussion leading to recommendations, please refer to the section linking the evidence to the recommendations (section 35.6, chapter 35).

M.3.6 WinBUGS code

M.3.6.1 WinBUGS code for assessment of baseline risk of DVT

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){           # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])                # Likelihood
   logit(p[i]) <- mu[i]                          # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)     # Random effects model
 }
mu.new ~ dnorm(m,tau.m)             # predictive dist. (log-odds)
m ~ dnorm(0,.0001)           # vague prior for mean
var.m <- 1/tau.m             # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)            # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m                # posterior probability of response
logit(R.new) <- mu.new        # predictive probability of response
}
Data
list(ns=22)  # ns=number of studies
r[]        n[]
6          24
11         48
14         51
```

11 97

4 118

12 412

21 50

17 39

10 50

20 61

13 33

4 57

11 97

17 52

37 103

6 44

23 47

4 92

15 33

11 31

9 41

14 88

END

Inits

list(mu=c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0), sd.m=1, m=0)

list(mu = c(-1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1), sd.m=2, m= -1)

list(mu = c(1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1), sd.m = 0.5, m = 1)

M.3.6.2 WinBUGS code for number of patients with DVT

#Random effects model for multi-arm trials (any number of arms)

model{

for(i in 1:NS){

w[i,1] <-0

```
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  sdev[i]<- sum(dev[i,1:na[i]])
  for (k in 2:na[i]){
# trial-specific LOR distributions
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <-sum(w[i,1:k-1])/(k-1)
   }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
sd ~ dunif(0,5)        # vague prior for random effects standard deviation
tau <- 1/pow(sd,2)

A ~ dnorm(meanA, precA)  # A is on log-odds scale
precA <- pow(sdA,-2)     # turn st dev into precision

for (k in 1:NT){        # v[1] will give prob of event on treat 1
  logit(v[k]) <- A + d[k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
```

```
 }
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lor[c,k] <- d[k] - d[c]
    log(or[c,k]) <- lor[c,k]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}

# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.

list(NS=48, NT=22, meanA=-1.371, sdA=1.105)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
6	24	6	28	2	29	1	2	3	3
11	48	3	49	3	48	1	2	4	3
14	51	6	46	NA	NA	1	2	NA	2
11	97	11	88	NA	NA	1	2	NA	2
4	118	1	108	NA	NA	1	2	NA	2
12	412	4	408	NA	NA	1	2	NA	2
21	50	4	48	NA	NA	1	2	NA	2

17	39	3	39	NA	NA	1	2	NA	2
10	50	3	50	NA	NA	1	2	NA	2
20	61	10	63	NA	NA	1	2	NA	2
13	33	3	31	NA	NA	1	2	NA	2
4	57	6	62	NA	NA	1	3	NA	2
11	97	14	97	NA	NA	1	3	NA	2
17	52	5	55	NA	NA	1	3	NA	2
37	103	15	97	NA	NA	1	5	NA	2
6	44	2	51	NA	NA	1	6	NA	2
23	47	11	48	NA	NA	1	7	NA	2
4.5	93	0.5	105	NA	NA	1	7	NA	2
15	33	6	33	NA	NA	1	8	NA	2
11	31	2	30	NA	NA	1	9	NA	2
9	41	3	39	NA	NA	1	10	NA	2
14	88	4	95	NA	NA	1	11	NA	2
6	107	3	101	NA	NA	2	3	NA	2
1	50	9	50	NA	NA	2	4	NA	2
7	429	16	431	7	430	2	11	12	3
7	190	6	195	NA	NA	2	11	NA	2
5	115	5	112	NA	NA	2	11	NA	2
1	72	2	74	NA	NA	2	11	NA	2
8	709	25	718	NA	NA	2	11	NA	2
41	497	28	505	NA	NA	2	12	NA	2
0.5	28	1.5	26	NA	NA	2	12	NA	2
9	217	13	215	NA	NA	2	12	NA	2
12	81	2	79	NA	NA	2	13	NA	2
7	90	1	86	NA	NA	2	13	NA	2
7	50	12	50	3	50	2	14	15	3
1.5	44	0.5	48	NA	NA	3	16	NA	2
0.5	54	2.5	48	NA	NA	4	16	NA	2
14	56	5	52	NA	NA	5	15	NA	2
1	58	3	56	NA	NA	6	7	NA	2

5 39 1 38 NA NA 7 17 NA 2

2.5 17 0.5 20 NA NA 11 12 NA 2

124 976 65 981 NA NA 11 12 NA 2

20 167 8 165 NA NA 12 18 NA 2

59 1018 43 1024 NA NA 12 19 NA 2

2 105 1 106 NA NA 12 20 NA 2

22 418 7 424 NA NA 20 21 NA 2

6 31 1 78 NA NA 20 22 NA 2

3.5 113 0.5 109 NA NA 20 22 NA 2

END

Inits

#chain 1

list(

d=c(NA,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0), # one for each treatment

sd=1,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2, -1,3,1,3,-2,-1,2,-2,3,-1, 1,-1,-2,-3,-1,-3,0,2,-1,-3, -2,1,1,3,-1,1,-2,-1,3,-2, -2,-3,1,-2,0,0,2,2))

#chain 2

list(

d=c(NA,-3,1,-1,-3, -1,-3,1,-1,-3, 1,-1,-2,-3,-1, -2,-1,2,-2,3, 0,0), # one for each treatment

sd=0.1,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2, -1,3,1,3,-2,-1,2,-2,3,-1, 1,-1,-2,-3,-1,-3,0,2,-1,-3, -2,1,1,3,-1,1,-2,-1,3,-2, -2,-3,1,-2,0,0,3,-2))

#chain 3

list(

d=c(NA,0,1,1,0, 0,0,0,1,2, 3,4,2,0,0, -2,-1,2,-2,3, 0,0), # one for each treatment

sd=2,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2, -1,3,1,3,-2,-1,2,-2,3,-1, 1,-1,-2,-3,-1,-3,0,2,-1,-3, -2,1,1,3,-1,1,-2,-1,3,-2, -2,-3,1,-2,0,0,1,-1))

M.3.6.3 WinBUGS code for inconsistency model for number of patients with DVT

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision
} # *** PROGRAM ENDS
```

Data

DVT

nt=no. treatments, ns=no. studies

list(nt=22,ns=48)

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
6	24	6	28	2	29	1	2	3	3
11	48	3	49	3	48	1	2	4	3
14	51	6	46	NA	NA	1	2	NA	2
11	97	11	88	NA	NA	1	2	NA	2
4	118	1	108	NA	NA	1	2	NA	2
12	412	4	408	NA	NA	1	2	NA	2
21	50	4	48	NA	NA	1	2	NA	2
17	39	3	39	NA	NA	1	2	NA	2
10	50	3	50	NA	NA	1	2	NA	2
20	61	10	63	NA	NA	1	2	NA	2
13	33	3	31	NA	NA	1	2	NA	2
4	57	6	62	NA	NA	1	3	NA	2
11	97	14	97	NA	NA	1	3	NA	2
17	52	5	55	NA	NA	1	3	NA	2
37	103	15	97	NA	NA	1	5	NA	2
6	44	2	51	NA	NA	1	6	NA	2
23	47	11	48	NA	NA	1	7	NA	2
4.5	93	0.5	105	NA	NA	1	7	NA	2
15	33	6	33	NA	NA	1	8	NA	2
11	31	2	30	NA	NA	1	9	NA	2
9	41	3	39	NA	NA	1	10	NA	2
14	88	4	95	NA	NA	1	11	NA	2
6	107	3	101	NA	NA	2	3	NA	2
1	50	9	50	NA	NA	2	4	NA	2
7	429	16	431	7	430	2	11	12	3
7	190	6	195	NA	NA	2	11	NA	2

5	115	5	112	NA	NA	2	11	NA	2
1	72	2	74	NA	NA	2	11	NA	2
8	709	25	718	NA	NA	2	11	NA	2
41	497	28	505	NA	NA	2	12	NA	2
0.5	28	1.5	26	NA	NA	2	12	NA	2
9	217	13	215	NA	NA	2	12	NA	2
12	81	2	79	NA	NA	2	13	NA	2
7	90	1	86	NA	NA	2	13	NA	2
7	50	12	50	3	50	2	14	15	3
1.5	44	0.5	48	NA	NA	3	16	NA	2
0.5	54	2.5	48	NA	NA	4	16	NA	2
14	56	5	52	NA	NA	5	15	NA	2
1	58	3	56	NA	NA	6	7	NA	2
5	39	1	38	NA	NA	7	17	NA	2
2.5	17	0.5	20	NA	NA	11	12	NA	2
124	976	65	981	NA	NA	11	12	NA	2
20	167	8	165	NA	NA	12	18	NA	2
59	1018	43	1024	NA	NA	12	19	NA	2
2	105	1	106	NA	NA	12	20	NA	2
22	418	7	424	NA	NA	20	21	NA	2
6	31	1	78	NA	NA	20	22	NA	2
3.5	113	0.5	109	NA	NA	20	22	NA	2

END

INITS

#chain 1

list(sd=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0,-3,-2,-3,-2, 3,-3,0,-1,-3, 2,1,3,-2,2, 2,0,1,2,0, 0,-2,0))

chain 2

list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1,-3,0,-3,0, 3,-3,1,-1,-3, 2,1,3,0,2, 2,1,1,2,1, 1,0,1))

chain 3

list(sd=3, mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5,-3,1,-3,1, 3,-3,0.5,-1,-3, 2,1,3,1,2, 2,0.5,1,2,0.5, 0.5,0,1))

M.3.6.4 WinBUGS code for assessment of baseline risk of PE

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){          # LOOP THROUGH STUDIES
  r[i] ~ dbin(p[i],n[i])              # Likelihood
  logit(p[i]) <- mu[i]                # Log-odds of response
  mu[i] ~ dnorm(m,tau.m)   # Random effects model
 }
mu.new ~ dnorm(m,tau.m)           # predictive dist. (log-odds)
m ~ dnorm(0,.0001)          # vague prior for mean
var.m <- 1/tau.m            # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)           # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m               # posterior probability of response
logit(R.new) <- mu.new      # predictive probability of response
}
Data
list(ns=11)  # ns=number of studies
r[]     n[]
1       97
1       52
1       24
0       50
1       17
0       97
24      54
```

```
2	61
1	41
2	88
1	47
END
 Inits
list(mu=c(0,0,0,0,0,   0,0,0,0,0,   0), sd.m=1, m=0)
list(mu = c(-1,-1,-1,-1,-1,   -1,-1,-1,-1,-1,   -1), sd.m=2, m= -1)
list(mu = c(1,1,1,1,1,   1,1,1,1,1,   1), sd.m = 0.5, m = 1)
```

M.3.6.5 WinBUGS code for number of patients with PE

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  sdev[i]<- sum(dev[i,1:na[i]])
  for (k in 2:na[i]){
# trial-specific LOR distributions
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
```

```
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
sd ~ dunif(0,5)       # vague prior for random effects standard deviation
tau <- 1/pow(sd,2)

A ~ dnorm(meanA, precA)  # A is on log-odds scale
precA <- pow(sdA,-2)     # turn st dev into precision

for (k in 1:NT){        # v[1] will give prob of event on treat 1
  logit(v[k]) <- A + d[k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lor[c,k] <- d[k] - d[c]
    log(or[c,k]) <- lor[c,k]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}
```

Data

NT=no. treatments, NS=no. studies;

NB : set up M vectors each r[,]. n[,] and t[,], where M is the Maximum number of treatments

per trial in the dataset. In this dataset M is 3.

list(NS=26, NT=13, meanA=-3.939, sdA=2.201)

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
1	97	4	97	NA	NA	1	2	NA	2
1	52	2	55	NA	NA	1	2	NA	2
1	24	1	29	1	28	1	2	3	3
0.5	51	2.5	49	NA	NA	1	3	NA	2
1.5	18	0.5	18	NA	NA	1	3	NA	2
0.5	98	4.5	89	NA	NA	1	3	NA	2
24	54	9	58	NA	NA	1	3	NA	2
2	61	1	63	NA	NA	1	3	NA	2
1.5	42	0.5	40	NA	NA	1	4	NA	2
2.5	89	0.5	96	NA	NA	1	5	NA	2
1.5	48	0.5	49	NA	NA	1	6	NA	2
0.5	44	1.5	48	NA	NA	2	7	NA	2
0.5	71	1.5	72	NA	NA	3	5	NA	2
1.5	191	0.5	196	NA	NA	3	5	NA	2
11	1915	8	1894	NA	NA	3	5	NA	2
1.5	73	0.5	75	NA	NA	3	5	NA	2
2	429	4	431	1	430	3	5	9	3
6	90	2	86	NA	NA	3	8	NA	2
4.5	498	0.5	506	NA	NA	3	9	NA	2
5.5	41	0.5	41	NA	NA	3	9	NA	2
0.5	469	1.5	469	NA	NA	3	9	NA	2
4	976	6	981	NA	NA	5	9	NA	2
1	39	1	38	NA	NA	6	10	NA	2
1.5	48	0.5	54	NA	NA	7	11	NA	2
2.5	168	0.5	166	NA	NA	9	12	NA	2
0.5	1463	2.5	1466	NA	NA	9	13	NA	2

```
END

Inits

#chain 1

list(

d=c(NA,0,0,0,0,   0,0,0,0,0,   0,0,0), # one for each treatment

sd=1,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2,    -1,3,1,3,-2,-1,2,-2,3,-1,   1,-1,-2,-3,-1,-3) )

#chain 2

list(

d=c(NA,-3,1,-1,-3,   -1,-3,1,-1,-3,   1,-1,-2), # one for each treatment

sd=0.1,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2,    -1,3,1,3,-2,-1,2,-2,3,-1,   1,-1,-2,-3,-1,-3) )

#chain 3

list(

d=c(NA,0,1,1,0,   0,0,0,1,2,   3,4,2), # one for each treatment

sd=2,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2,    -1,3,1,3,-2,-1,2,-2,3,-1,   1,-1,-2,-3,-1,-3) )
```

M.3.6.6 WinBUGS code for inconsistency model for number of patients with PE

```
# Binomial likelihood, logit link, inconsistency model

# Random effects model

model{                    # *** PROGRAM STARTS

for(i in 1:ns){           # LOOP THROUGH STUDIES

   delta[i,1]<-0          # treatment effect is zero in control arm

   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines

   for (k in 1:na[i])  {   # LOOP THROUGH ARMS

      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood

      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor

#Deviance contribution

      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators

      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))

       +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
```

```
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision
} # *** PROGRAM ENDS
```

Data

DVT

nt=no. treatments, ns=no. studies

list(nt=13,ns=26)

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
1	97	4	97	NA	NA	1	2	NA	2
1	52	2	55	NA	NA	1	2	NA	2
1	24	1	29	1	28	1	2	3	3
0.5	51	2.5	49	NA	NA	1	3	NA	2
1.5	18	0.5	18	NA	NA	1	3	NA	2
0.5	98	4.5	89	NA	NA	1	3	NA	2
24	54	9	58	NA	NA	1	3	NA	2
2	61	1	63	NA	NA	1	3	NA	2
1.5	42	0.5	40	NA	NA	1	4	NA	2
2.5	89	0.5	96	NA	NA	1	5	NA	2

1.5	48	0.5	49	NA	NA	1	6	NA	2
0.5	44	1.5	48	NA	NA	2	7	NA	2
0.5	71	1.5	72	NA	NA	3	5	NA	2
1.5	191	0.5	196	NA	NA	3	5	NA	2
11	1915	8	1894	NA	NA	3	5	NA	2
1.5	73	0.5	75	NA	NA	3	5	NA	2
2	429	4	431	1	430	3	5	9	3
6	90	2	86	NA	NA	3	8	NA	2
4.5	498	0.5	506	NA	NA	3	9	NA	2
5.5	41	0.5	41	NA	NA	3	9	NA	2
0.5	469	1.5	469	NA	NA	3	9	NA	2
4	976	6	981	NA	NA	5	9	NA	2
1	39	1	38	NA	NA	6	10	NA	2
1.5	48	0.5	54	NA	NA	7	11	NA	2
2.5	168	0.5	166	NA	NA	9	12	NA	2
0.5	1463	2.5	1466	NA	NA	9	13	NA	2

END

INITS

#chain 1

list(sd=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0))

chain 2

list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1))

chain 3

list(sd=3, mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5))

M.3.6.7 WinBUGS code for assessment of baseline risk of major bleeding

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){          # LOOP THROUGH STUDIES
  r[i] ~ dbin(p[i],n[i])          # Likelihood
```

```
   logit(p[i]) <- mu[i]                    # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)      # Random effects model
 }
mu.new ~ dnorm(m,tau.m)              # predictive dist. (log-odds)
m ~ dnorm(0,.0001)            # vague prior for mean
var.m <- 1/tau.m              # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)             # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m                 # posterior probability of response
logit(R.new) <- mu.new        # predictive probability of response
}
 Data

list(ns=10)  # ns=number of studies
r[]        n[]
4          88
0          25
0          30
0          17
23         61
0          41
1          14
1          38
0          112
1          650
END
 Inits
list(mu=c(0,0,0,0,0,   0,0,0,0,0), sd.m=1, m=0)
list(mu = c(-1,-1,-1,-1,-1,   -1,-1,-1,-1,-1), sd.m=2, m= -1)
list(mu = c(1,1,1,1,1,   1,1,1,1,1), sd.m = 0.5, m = 1)
```

M.3.6.8 WinBUGS code for number of patients with major bleeding

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  sdev[i]<- sum(dev[i,1:na[i]])
  for (k in 2:na[i]){
# trial-specific LOR distributions
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <-sum(w[i,1:k-1])/(k-1)
   }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
sd ~ dunif(0,5)        # vague prior for random effects standard deviation
tau <- 1/pow(sd,2)

A ~ dnorm(meanA, precA)  # A is on log-odds scale
```

```
precA <- pow(sdA,-2)     # turn st dev into precision


for (k in 1:NT){        # v[1] will give prob of event on treat 1
  logit(v[k]) <- A + d[k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lor[c,k] <- d[k] - d[c]
    log(or[c,k]) <- lor[c,k]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}
```

Data

```
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#        per trial in the dataset. In this dataset M is 3.
list(NS=29, NT=8, meanA=-5.331 sdA=3.482)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
4	88	4	95	NA	NA	1	2	NA	2
0.5	26	0.5	26	1.5	26	1	3	4	3
0.5	31	6.5	31	NA	NA	1	3	NA	2
0.5	18	1.5	18	NA	NA	1	3	NA	2

23	61	24	63	NA	NA	1	3	NA	2
0.5	42	1.5	40	NA	NA	1	4	NA	2
1	14	2	16	NA	NA	1	4	NA	2
1	38	5	109	NA	NA	1	4	NA	2
0.5	113	2.5	109	NA	NA	1	4	NA	2
1	650	10	635	NA	NA	1	5	NA	2
14	71	9	70	NA	NA	2	3	NA	2
0.5	38	6.5	32	NA	NA	2	3	NA	2
69	1894	91	1915	NA	NA	2	3	NA	2
17	74	23	72	NA	NA	2	3	NA	2
14	431	12	429	10	430	2	3	6	3
2	112	15	115	NA	NA	2	3	NA	2
11	725	18	719	NA	NA	2	3	NA	2
3	1034	13	1036	NA	NA	2	6	NA	2
0.5	17	1.5	20	NA	NA	2	6	NA	2
2	217	10	215	NA	NA	3	6	NA	2
13	110	32	105	NA	NA	3	6	NA	2
1	40	2	40	NA	NA	3	6	NA	2
5.5	83	0.5	85	NA	NA	3	6	NA	2
10	643	18	653	NA	NA	3	6	NA	2
1	27	1	25	NA	NA	3	6	NA	2
1	20	6	23	NA	NA	3	7	NA	2
49	1433	34	1425	NA	NA	5	6	NA	2
1	248	3	253	NA	NA	6	8	NA	2
4	222	1	205	NA	NA	6	8	NA	2

END

Inits

#chain 1

list(

d=c(NA,0,0,0,0, 0,0,0), # one for each treatment

sd=1,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2, -1,3,1,3,-2,-1,2,-2,3,-1, 1,-1,-2,-3,-1,-3,0,2,1))

```
#chain 2
list(
d=c(NA,-3,1,-1,-3,   -1,-3,1), # one for each treatment
sd=0.1,
mu=c(3,2,-3,1,0,3,-2,-1,2,-2,    -1,3,1,3,-2,-1,2,-2,3,-1,   1,-1,-2,-3,-1,-3,0,2,3) )
#chain 3
list(
d=c(NA,0,1,1,0,   0,0,0), # one for each treatment
sd=2,
mu=c(3,2,-3,1,0,3,-2,-1,2,-2,    -1,3,1,3,-2,-1,2,-2,3,-1,   1,-1,-2,-3,-1,-3,0,2,0) )
```

M.3.6.9 WinBUGS code for inconsistency model for number of patients with major bleeding

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){           # LOOP THROUGH STUDIES
   delta[i,1]<-0          # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
```

```
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision
} # *** PROGRAM ENDS
```

Data

```
# Major bleeding
# nt=no. treatments, ns=no. studies
list(nt=8,ns=29)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
4	88	4	95	NA	NA	1	2	NA	2
0.5	26	0.5	26	1.5	26	1	3	4	3
0.5	31	6.5	31	NA	NA	1	3	NA	2
0.5	18	1.5	18	NA	NA	1	3	NA	2
23	61	24	63	NA	NA	1	3	NA	2
0.5	42	1.5	40	NA	NA	1	4	NA	2
1	14	2	16	NA	NA	1	4	NA	2
1	38	5	109	NA	NA	1	4	NA	2
0.5	113	2.5	109	NA	NA	1	4	NA	2
1	650	10	635	NA	NA	1	5	NA	2
14	71	9	70	NA	NA	2	3	NA	2
0.5	38	6.5	32	NA	NA	2	3	NA	2
69	1894	91	1915	NA	NA	2	3	NA	2
17	74	23	72	NA	NA	2	3	NA	2
14	431	12	429	10	430	2	3	6	3

2 112 15 115 NA NA 2 3 NA 2

11 725 18 719 NA NA 2 3 NA 2

3 1034 13 1036 NA NA 2 6 NA 2

0.5 17 1.5 20 NA NA 2 6 NA 2

2 217 10 215 NA NA 3 6 NA 2

13 110 32 105 NA NA 3 6 NA 2

1 40 2 40 NA NA 3 6 NA 2

5.5 83 0.5 85 NA NA 3 6 NA 2

10 643 18 653 NA NA 3 6 NA 2

1 27 1 25 NA NA 3 6 NA 2

1 20 6 23 NA NA 3 7 NA 2

49 1433 34 1425 NA NA 5 6 NA 2

1 248 3 253 NA NA 6 8 NA 2

4 222 1 205 NA NA 6 8 NA 2

END

INITS

#chain 1

list(sd=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0,-3,-2,-3))

chain 2

list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1,-3,0,-3))

chain 3

list(sd=3, mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5,-3,1,-3))

Appendix N: Excluded clinical studies

N.1 Risk assessment

Study	Exclusion reason
Abdel-Razeq 2010 [1]	Model not appropriately validated
Abdul Sultan 2013 [4]	Comparison does not match protocol
Abdul Sultan 2013 [3]	Comparison does not match protocol
Abumuaileq 2015 [8]	No relevant statistical outcomes reported
Acuna 2011 [9]	No relevant statistical outcomes reported
Ahn 2013 [17]	Incorrect population
Al-Ani 2015[25]	Incorrect study design
Ali 2017 [31]	Incorrect study design
Aminian 2017 [38]	Model not appropriately validated
Arcelus 1991 [46]	No relevant statistical outcomes reported
Arrigo 2011[48]	No relevant statistical outcomes reported
Ay 2011[58]	Model not appropriately validated
Bagaria 2011 [63]	Comparison does not match protocol
Barbar 2010[70]	No relevant statistical outcomes reported
Barber 2016 [71]	Study design does not match protocol
Barr 2014 [73]	Incorrect population
Basta 2016 [76]	Prognostic tool does not match protocol
Bauersachs 2007 [80]	Comparison does not match protocol
Bekelis 2014a [86]	Model not appropriately validated
Bekelis 2014b[88]	Model not appropriately validated
Bekelis 2015[87]	Model not appropriately validated
Berkin 2016 [94]	Prognostic tool does not match protocol
Beyth 1998[98]	Incorrect population
Bikdeli 2013[99]	Incorrect study design
Bilgi 2016 [100]	Prognostic tool does not match protocol
Bircan 2011[102]	Incorrect study design
Blondon 2017 [107]	Incorrect study design
Bogari 2014[114]	No relevant statistical outcomes reported
Bohl 2016 [115]	Model not appropriately validated
Calisir 2009[143]	Incorrect study design
Campbell 2013 [145]	Incorrect study design
Caprini 1991[151]	No relevant statistical outcomes reported
Caprini 2001 [152]	Literature review
Caprini 2005[150]	Incorrect study design
Carpenter 2009[154]	No relevant statistical outcomes reported
Cavazza 2012[162]	Incorrect comparison
Chagnon 2002[163]	Incorrect study design
Chatterjee 2017 [168]	Incorrect study design

Study	Exclusion reason
Chauleur 2008[169]	No relevant statistical outcomes reported
Chen 2006[172]	Incorrect study design
Child 2013 [176]	No relevant statistical outcomes reported
Cohen 2005[190]	Incorrect study design
Cohen 2009 [198]	No relevant statistical outcomes reported
Cohen 2014[193]	Incorrect study design
Coleman 2016 [200]	Population does not match protocol
Constans 2003[211]	Incorrect population
Cornuz 2002[214]	Incorrect study design
Correia 2012[215]	Incorrect study design
Couture 2016 [220]	Insufficient data - abstract only
Crane 2016 [221]	Incorrect study design
Creagh 2013 [222]	Comparison does not match protocol
Dargaud 2005[231]	Incorrect study design
Dargaud 2009[232]	Incorrect population
de Bastos 2016 [237]	Model not appropriately validated
Decousus 2011 [243]	Incorrect study design
Desai 2016 [251]	Insufficient data - abstract only
Di Marca 2015[253]	Incorrect study design
Di Nisio 2017 [256]	Population does not match protocol
Dietch 2015[259]	Model not appropriately validated
Dronkers 2016 [271]	Prognostic tool does not match protocol
Eckman 2003[274]	Incorrect study design
Eichinger 2010[277]	Incorrect population
Eichinger 2014[278]	Incorrect population
Elf 2009[282]	Incorrect study design
Elsasser 2007[284]	Incorrect study design
Elton 2015 [285]	Comparison does not match protocol
Erkens 2012[296]	Incorrect population
Evans 2007[298]	Model not appropriately validated
Evans 2010[299]	Model not appropriately validated
Fang 2011[300]	Incorrect population
Finks 2012[304]	Model not appropriately validated
Flanders 2014 [309]	Incorrect study design
Franco Moreno 2016 [316]	Population does not match protocol
Gage 2006[330]	Incorrect population
Galanter 2010 [331]	Not appropriately validated
Gallagher 2009 [333]	Not appropriately validated
Gearhart 2000[339]	No relevant statistical outcomes reported
Gerotziafas 2017 [342]	Incorrect study design
Gibson 2008[345]	Incorrect study design
Gibson 2014 [343]	Comparison does not match protocol
Goergen 2005[348]	Incorrect study design

Study	Exclusion reason
Goffman 2009 [349]	Comparison does not match protocol
Gould 2012 [356]	Incorrect study design
Grant 2016 [358]	Insufficient data reported
Greenfield 1997 [361]	Model not appropriately validated
Grille 2015 [362]	Comparison does not match protocol
Gronberg 2016 [363]	Target condition does not match protocol
Gruettner 2015[365]	Incorrect study design
Haas 2006[369]	No relevant statistical outcomes reported
Haas 2007[370]	No relevant statistical outcomes reported
Hachey 2015[415]	Incorrect population
Hachey 2016 [372]	Study design does not match protocol
Hack 2012 [373]	Comparison does not match protocol
Haider 2016 [375]	Population does not match protocol
Hairon 2008[376]	Incorrect study design
Haque 2016 [388]	Model not appropriately validated
Harinath 1998 [392]	Tool not appropriately validated
Harris 2016 [393]	Comparison does not match protocol
Heath 2016 [402]	Comparison does not match protocol
Heinemann, 2005 [409]	No relevant statistical outcomes reported
Hendriksen 2015[414]	Incorrect study design
Hippisley-Cox 2011[418]	Target condition does not match protocol
Hippisley-Cox 2014[419]	Target condition does not match protocol
Hohl Moinat 2014[428]	No relevant statistical outcomes reported
Huang 2013[434]	Systematic review – checked for references
Ismail 2015 [447]	Comparison does not match protocol
Jacobson 2014 [449]	No relevant outcomes
Janssen 2012[454]	Model not appropriately validated
Johnson 1999[457]	Model not appropriately validated
Kabrhel 2005[461]	Incorrect study design
Kafeza 2016 [462]	Incorrect study design
Karamat 2017 [475]	Incorrect study design
Katsios 2014[476]	Incorrect study design
Katz 2017 [477]	Does not match guideline condition
Kawaguchi 2013 [478]	Model not appropriately validated
Kearon 2003[480]	Incorrect population
Khairy 2016 [484]	Study design does not match protocol
Klok 2008 [498]	Incorrect study design
Klok 2016[499]	Incorrect population
Kooiman 2015[502]	Target condition does not match protocol
Kucher 2005[513]	Model not appropriately validated
Kuderer 2016 [514]	Target condition does not match protocol
Kuijer 1999[515]	Incorrect population
Kurtoglu 2011 [517]	Incorrect study design

Study	Exclusion reason
La Regina 2016 [520]	No relevant statistical outcomes reported
Landefeld 1989[522]	Incorrect study design
Lankeit 2013[523]	Risk factors only
Le Gal 2006 [541]	Incorrect study design
Liew 2016 [559]	Incorrect study design
Lindqvist 2002 [566]	Comparison does not match protocol
Lindqvist 2008 [567]	Incorrect study design
Lindqvist 2011 [565]	Incorrect study design
Liu 2013[571]	No relevant statistical outcomes reported
Liu 2016 [570]	Incorrect study design
Louzada 2012[580]	No relevant statistical outcomes reported
Lyle 2016 [588]	Prognostic tool does not match protocol
Macht 2017 [596]	Incorrect study design
Maestre 2015 [599]	Incorrect study design
Mahan 2014 [600]	Incorrect population
Mansfield 2016 [605]	Incorrect study design
Manson 2014 [606]	Incorrect intervention
Maynard 2010[614]	No relevant statistical outcomes reported
McAlister 2016 [616]	Does not meet guideline condition
McAlpine 2017 [617]	Prognostic tool does not match protocol
McCaffrey 2007[619]	No relevant statistical outcomes reported
McGoldrick 2016 [623]	Incorrect study design
Mearns 2010[628]	Incorrect study design
Meizoso 2017 [630]	Model not appropriately validated
Meyer 2015 [636]	Incorrect study design
Miron 2000[643]	Incorrect study design
Modi 2016 [649]	Incorrect study design
Mokhtari 2014[650]	Risk factors only
Mueller 2016 [659]	Population does not match protocol
Nam 2016 [665]	Prognostic tool does not match protocol
Navarro 2016 [679]	Population does not match protocol
Nemeth 2015[680]	Incorrect study design
Nendaz 2004[681]	No relevant outcomes reported
Nieto 2013 [687]	Incorrect population
Novis 2010 [701]	Not appropriately validated
O'Connor 2011 [704]	Incorrect study design
Okumus 2009[710]	No relevant statistical outcomes reported
Olesen 2011[711]	Incorrect target condition
Olesen 2012[712]	Target condition does not match protocol
Ollenberger 2006 [713]	Incorrect study design
Ongen 2015 [714]	Incorrect study design
Oz 2016 [718]	Incorrect study design
Pai 2013 [721]	No relevant outcomes reported

Study	Exclusion reason
Pannucci 2011[726]	No relevant statistical outcomes reported
Pannucci 2012[727]	No relevant statistical outcomes reported
Pannucci 2013 [725]	Insufficient data - abstract only
Pannucci 2015[728]	Tool not appropriately validated
Pannucci 2017 [729]	Systematic review - checked for references
Parilla 2016 [730]	Incorrect study design
Parilla 2016 [730]	Comparison does not match protocol
Patel 2016 [732]	Does not meet guideline condition
Penaloza 2010[739]	Incorrect study design
Philippart 2015 [747]	Does not meet guideline condition
Piazza 2009[749]	Model not appropriately validated
Piovella 2014[753]	Incorrect population
Pisters 2010[754]	Incorrect population
Press 2015 [773]	Abstract only
Ramos 2016 [786]	Incorrect study design
Righini 2013 [803]	Setting does not match protocol
Rivard 2016 [806]	Prognostic tool does not match protocol
Rocha 2007[812]	Risk factors only
Rosenburg 2014[821]	Incorrect study design
Ruiz-Gimenez 2008[829]	Incorrect population
Ruiz-Gimenez[829]	Incorrect population
Ruttimann 2005 [831]	Not appropriately validated
Samama 2006 [847]	Model not appropriately validated
Santos 2015 [852]	Insufficient data reported
Sarela 2011[854]	No relevant statistical outcomes reported
Sarkar 2013 [855]	Incorrect study design
Scherz 2013 [861]	Incorrect population
Schneider 2016 [864]	Prognostic tool does not match protocol
Schoenbeck 2011 [865]	Tool not appropriately validated
Schouten 2014 [866]	Incorrect study design
Sermsathanasawadi 2015 [876]	Incorrect study design
Shen 2016 [882]	Incorrecty study design
Shlebak 2016 [884]	Incorrecty study design
Shuman 2012 [888]	No relevant statistical outcomes reported
Silveira 2015[890]	Incorrect study design
Soomro 2014[908]	Risk factors only
Spyropoulos 2011[913]	Incorrect population
Spyropoulos 2012[914]	Literature review
Stroud 2014[925]	No relevant statistical outcomes reported
Stuck 2017 [926]	Incorrect study design
Tamizifar 2016 [931]	Incorrect study design
Testa 2013 [934]	Setting does not match protocol
Tomkowski 2011[940]	No relevant statistical outcomes reported

Study	Exclusion reason
Van der Pol 2016 [962]	Comparison does not match protocol
van Es 2017 [966]	Incorrect study design
Vazquez-Acosta 2016 [970]	Not in English
Wang 2016 [986]	Does not meet guideline condition
Watson 2016 [998]	Incorrect study design
Weill-Engerer 2004 [1000]	Risk factors only
Wells 2003[1004]	Population does not match protocol
Xing 2016 [1025]	Does not meet guideline condition
Yarlagadda 2014[1027]	No relevant statistical outcomes reported
Young 2013[1033]	Incorrect study design
Zakai 2013[1038]	Tool not appropriately validated
Zhou 2012[1046]	No relevant statistical outcomes reported
Zhou 2014 [1045]	Incorrect study design
Zhu 2017 [1048]	Does not meet guideline condition
Zilio 2016 [1050]	Prognostic tool does not match protocol

N.2 Patient information

Reference	Reason for exclusion
Alonso-Coello 2012[32]	Protocol only
Amara 2016	Incorrect study design
Bouman 2016[122]	Population does not match protocol as patients did not receive prophylaxis
Brekelmans 2017[127]	Population does not match protocol as patients did not receive prophylaxis
Haxaire 2015[398]	Research question does not match protocol as focus is on VTE risk factors not thromboprophylaxis
Hunter 2016[443]	Population does not match protocol as patients did not receive prophylaxis
Kresec 2011[511]	Abstract only
McLean 2010[625]	Systematic review checked for references; population does not match protocol
Mockler 2012[648]	Population does not match protocol
Noble 2008[698]	Research question does not match protocol
Noble 2014[692]	Population does not match protocol as patients did not receive prophylaxis
Noble 2014[696]	Abstract only
Noble 2014[697]	Abstract only
Noble 2015[693]	Abstract only
Noble 2015[695]	Population does not match protocol as patients did not receive prophylaxis
Noble 2015[694]	Incorrect study design
Nordenholz 2015[699]	Abstract only
Seaman 2014[875]	Population does not match protocol as patients did not receive

Reference	Reason for exclusion
	prophylaxis
Sheard 2012[879]	Population does not match protocol as patients did not receive prophylaxis
Sheard 2012[880]	Population does not match protocol as patients did not receive prophylaxis
Wild 2009[1008]	Population does not match protocol as patients did not receive prophylaxis
Wong 2013[1020]	Abstract only
Wong 2015[1019]	Incorrect study design (questionnaire study)

N.3 VTE prophylaxis

Reference	Reason for exclusion
Abdelkefi 2004 [2]	Incorrect population
Abdul 2013 [3]	Incorrect study design
Abdulhak 2013 [101]	Systematic review checked for references
Abernethy 1974[5]	Incorrect population
Abraham-Inpijn1975[7]	Incorrect population
Abraham-Inpijn1979[6]	Incorrect population
ACOG 2011 [36]	Incorrect study design
Adam 2013 [10]	Systematic review checked for references
Adolf 1989[11]	Not in English
Agarwal 2010 [12]	Systematic review checked for references
Agnelli 1998[15]	Incorrect population
Agnelli 2012 [14]	Intervention does not match protocol.
Agnelli 2013 [13]	Incorrect population
Agnelli 2015 [16]	Incorrect study design
Akhtar 2014 [18]	No relevant outcomes reported
Akl 2007 [21]	Systematic review checked for references
Akl 2008 [23]	Systematic review checked for references
Akl 2008 [24]	Systematic review checked for references
Akl 2014 [22]	Systematic review checked for references
Akl 2014 [19]	Systematic review checked for references
Akl 2014 [20]	Systematic review checked for references
Alalaf 2015 [27]	Incorrect study design
Alalaf 2015 [26]	Intervention does not match protocol
Albertsen 2012 [28]	Systematic review checked for references
Alfaro 1986 [29]	Intervention does not match protocol
Alhazzani 2013 [30]	Systematic review checked for references
Alotaibi 2014 [33]	Incorrect population
Altinbas 2004 [34]	Does not meet guideline condition
Amin 2009 [37]	Incorrect study design
Anderson 2013 [39]	Incorrect study design – commentary
Anon 2008 [581]	Abstract only

Reference	Reason for exclusion
Anon 2012 [958]	No relevant outcomes reported
Anon 2013 [591]	No relevant outcomes reported
Anon 2014 [982]	No relevant outcomes reported
Antiplatelet 1994 [201]	Systematic review checked for references
Antiplatelet Trialists' Collaboration 1994 [42]	Incorrect intervention
Antolovic 2012 [43]	Incorrect study design
Arabi 2013 [45]	Incorrect study design
Arabi 2016 [44]	Incorrect study design
Arnold 2010 [47]	Incorrect study design
Aryal 2014 [50]	Systematic review checked for references
Aryal 2015 [49]	Systematic review checked for references
Assadian 2008 [52]	No relevant outcomes reported
As-Sultany 2013 [51]	Systematic review checked for references
Atiq 2015 [53]	No relevant outcomes reported
Attaran 2010 [54]	No relevant outcomes reported
Auer 2011 [55]	Incorrect study design
Avidan 2011 [56]	No relevant outcomes reported
Ayhan 2013 [59]	Incorrect population
Ayhan 2015 [60]	No relevant outcomes reported
Bachmann 1976[62]	Incorrect population
Bain 2014[64]	Systematic review checked for references
Bakirhan 2013[66]	Incorrect study design
Balas 1992 [67]	Incorrect population
Bamber 2013 [68]	Incorrect population
Bani-Hani 2008 [69]	Systematic review checked for references
Barbui 1990[72]	Conference abstract
Barrellier 2010 [74]	Intervention did not match protocol
Barrera 2013 [75]	Systematic review checked for references
Bath 2009 [77]	Incorrect study design
Bauersachs 2011 [79]	Incorrect population
Baumgartner 1989[81]	Incorrect intervention
Becattini 2012 [83]	Systematic review checked for references
Beghi 1993[84]	Incorrect intervention
Beitland 2015 [85]	Systematic review checked for references
Belch 1980 [89]	Intervention does not match protocol
Ben-Aharon 2014 [90]	Systematic review checked for references
Bergmann 1996 [91]	Incorrect study design
Bergqvist 1979 [93]	Incorrect population
Bern 2002[95]	Incorrect intervention
Bern 2010 [96]	Abstract only
Beyer-Westendorf [97]	Abstract only
Blackshear 1987[105]	Incorrect population

Reference	Reason for exclusion
Bloom 2014 [108]	Incorrect population
Bockheim 2009 [110]	Does not meet guideline condition
Boehringer 2012 [112]	Incorrect study design
Boese 2014 [113]	No relevant outcomes
Boneu 1993[116]	Incorrect population
Bookhart 2014 [117]	Incorrect population
Borgstrom 1965 [118]	Incorrect intervention
Borris 2010 [119]	Abstract
Bottaro 2008 [120]	Systematic review checked for references
Boutros 2008 [123]	Incorrect study design
Bozas 2016 [124]	Incorrect study design
Bramlage 2012 [126]	Incorrect comparison
Breuer 2013 [128]	Incorrect study design
Briel 1988[129]	Not in English
Brismar 1982 [130]	No relevant outcomes reported
Brotman 2013 [132]	Systematic review checked for references
Brown 2009 [133]	Systematic review checked for references
Brown 2014 [134]	Incorrect population
Bruins 2014 [135]	Incorrect study design
Bruun-Olsen 2009 [136]	No relevant outcomes reported
Bump 2009 [137]	Systematic review checked for references
Bushwitz 2010 [138]	Abstract
Bynke 1987[139]	Inappropriate comparison
Cadth 2013 [141]	Systematic review checked for references
Cadth 2013 [140]	Incorrect study design
Cadth 2013 [142]	Incorrect study design
Camporese 2008 [146]	Incorrect study design
Cappato 2014 [147]	No relevant outcomes reported
Cappato 2015 [148]	Incorrect population
Carrier 2010 [155]	Incorrect study design
Carson 2012 [156]	Incorrect study design
Casele 2006[157]	Incorrect population
Casella 2015 [158]	Incorrect study design
Castellano 2016 [159]	No relevant outcomes reported
Catania 1988[160]	Incorrect intervention
Cavallo 2010 [161]	Abstract only
Chahinian 1989 [164]	Does not meet guideline condition
Chan 2015 [166]	Systematic review checked for references
Chapelle 2014 [167]	Systematic review checked for references
Che 2013 [170]	Systematic review checked for references
Chelladurai 2013 [171]	Systematic review checked for references
Chen 2012 [173]	Incorrect population
Cheng 2011 [174]	Intervention does not match protocol

Reference	Reason for exclusion
Cho 2013 [178]	Incorrect population
Choi 2014 [179]	No relevant outcomes reported
Christensen 2017 [180]	No relevant outcomes reported
Chunilal 2011 [626]	Incorrect study design
Clark 1974[181]	Incorrect intervention
Clemens 2012 [182]	Incorrect study design
CLOTS 2009 [187]	Incorrect population
CLOTS 2010 [183]	Incorrect population
CLOTS 2013 [186]	Incorrect population
CLOTS 2013 [185]	Incorrect population
CLOTS 2014 [184]	Incorrect study design
Cohen 2011 [195]	Incorrect study design
Cohen 2011 [196]	No relevant outcomes reported
Cohen 2012 [188]	Systematic review checked for references
Cohen 2015 [191]	Abstract only
Cohen 2015 [197]	Incorrect population
Cohen 2015 [189]	Incorrect population
Cohen 2015 [194]	Systematic review checked for references
Cohn 1999 [199]	Incorrect population
Collen 2008 [202]	Systematic review checked for references
Cologhera 1984[144]	Not in English
Colwell 2014 [206]	Incorrect study design
Connolly 2009 [210]	Incorrect population
Cornette 2002[213]	Incorrect intervention
Cosmi 2012 [216]	Incorrect population
Costa 2009 [218]	Incorrect population
Couban 2005[219]	Incorrect intervention
Cui 2014 [223]	Systematic review checked for references
Dal Molin 2014 [229]	Does not meet guideline condition
Dar 2012 [230]	Incorrect study design
Datta 2010 [233]	Systematic review checked for references
Davies 2016 [235]	Systematic review checked for references
De 2010 [236]	Incorrect population
De Veciana 2001[238]	Conference abstract
Dechavanne 1974 [239]	Non-English
Dechavanne 1975[241]	Incorrect population
Dechavanne 1989 [240]	Incorrect intervention
Decousus 1998[242]	Does not match guideline condition
Deeks 2012 [244]	Systematic review checked for references
Den Ottolander 1972 [246]	Incorrect study design
Der Veen 2013 [963]	Incorrect study design
Desai 2012 [839]	Systematic review checked for references
Diaz 2015 [258]	Abstract only

Reference	Reason for exclusion
Di Biase 2014 [252]	Incorrect population
Di Nisio 2014 [255]	Systematic review checked for references
Di Nisio 2015 [254]	Systematic review checked for references
DiSerio 1985[260]	Incorrect population
Dong 2011 [261]	Incorrect population
Dong 2016 [262]	Systematic review checked for references
Dooley 2013 [263]	Systematic review checked for references
Douketis 2008 [264]	No relevant outcomes reported
Douketis 2015 [265]	Intervention does not match protocol
Dranitsaris 2012 [266]	Incorrect population
Dranitsaris 2017 [268]	Incorrect population
Drescher 2014 [270]	Systematic review checked for references
Edwards 2008 [275]	Incorrect study design
Eikelboom 2009 [280]	Systematic review checked for references
Eikelboom 2016 [279]	Systematic review checked for references
Elbadawi 2017 [281]	Systematic review checked for references
Elit 2012 [283]	Does not meet guideline condition
Encke 1976[286]	Incorrect intervention
Eppsteiner 2009 [1016]	Systematic review checked for references
Eriksson 2006[290]	Incorrect intervention
Eriksson 2009 [294]	Incorrect study design
Eriksson 2010 [295]	Incorrect intervention
Eskander 1997 [297]	Incorrect intervention
Feller 1992[302]	Incorrect population
Feng 2015 [303]	Systematic review checked for references
Finnish Medical Society Duodecim 2013 [306]	Incorrect study design
Finnish Medical Society Duodecim 2014 [305]	Incorrect study design
Fisher 2013 [307]	Incorrect intervention
Flicoteaux 1977 [310]	Incorrect intervention
Fordyce 1991[311]	Incorrect population
Fraisse 2000 [313]	Incorrect population
Francis 1996 [314]	Incorrect comparison
Freeman 2012[317]	Incorrect study design
Freick 1991 [318]	Incorrect intervention
Friedman 1994[319]	Incorrect population
Fuji 2010 [326]	Incorrect comparison
Fuji 2012 [327]	Incorrect intervention
Fuji 2014 [323]	Incorrect intervention
Fuji 2014 [329]	Incorrect comparison
Fuji 2015 [322]	Incorrect comparison
Fuji 2015 [321]	Incorrect intervention
Fuji 2016 [324]	Incorrect intervention

Reference	Reason for exclusion
Garcea 1992[335]	Incorrect intervention
Garcia 2011 [212]	Abstract only
Gardlund 1996 [61]	Incorrect population
Gates 2002[337]	Systematic review checked for references
Gates 2004 [336]	Outcome does not match protocol
Gazzaniga 1993[338]	Incorrect population
Gerhart 1991[341]	Incorrect population
GHAT 1992 [937]	Incorrect intervention
Gibson 1998[344]	Incorrect intervention
Godwin 1993[346]	Incorrect intervention
Goel 2008 [347]	Incorrect population
Gomes 2011 [350]	Incorrect comparison
Green 1982[359]	Incorrect intervention
Green 2010 [360]	Incorrect study design
Groote Shuur Hospital Thromboembolus Study Group 1979[364]	Incorrect population
Group 1975 [974]	Incorrect population
Haas 1987 [367]	Incorrect intervention
Haas 1990 [368]	Incorrect intervention
Haas 1999[371]	Conference abstract
Haas 2012 [366]	Incorrect study design
Hajibandeh 2015 [377]	Incorrect study design
Hamel-Desnos 2009 [378]	Incorrect intervention
Hamersley 1998[379]	Conference abstract
Hamidi 2014 [380]	Incorrect population
Hamulyak 1995[383]	Incorrect population
Handley 1972 [384]	Incorrect intervention
Handley 1972 [385]	Intervention does not match protocol
Hanison 2016 [386]	Incorrect study design
Hansberry 1991[387]	Incorrect population
Harenberg 1990 [390]	Incorrect intervention
Harenberg 1993[391]	Incorrect intervention
Harris 1974 [382]	Incorrect intervention
Harris 1977 [395]	Incorrect intervention
Harris 1985 [394]	Incorrect intervention
Hata 2014 [396]	Incorrect study design
Haut 2014 [397]	Systematic review checked for references
Healey 2012 [400]	Incorrect study design
Heaton 2002[403]	Incorrect intervention
Heit 1997[411]	Incorrect intervention
Hedlund 1979[404]	Incorrect population
Hedlund 1981[405]	Incorrect population
Heilmann 1989[407]	Incorrect population

Reference	Reason for exclusion
Heilmann 1991[406]	Not in English
Heilmann 1998[408]	Incorrect population
Heit 1997[411]	Incorrect population
Heit 2000 [410]	Incorrect intervention
Helviz 2016 [413]	Incorrect intervention
Hill 1988[416]	No relevant outcomes
Hills 1972[417]	Incorrect study design
Hirschl 2014 [420]	Incorrect population
Ho 1999 [423]	Outcome measure does not match protocol
Ho 2013 [422]	Systematic review checked for references
Ho 2015 [421]	Systematic review checked for references
Hochhegger 2014 [424]	No relevant outcomes reported
Hoffman 1990[425]	Incorrect study design
Hoffmann 1992[426]	Incorrect study design
Hoffmeyer 2017 [427]	Incorrect study design
Holley 2012 [429]	Incorrect study design
Holmes 2012 [430]	Incorrect study design
Hossain Shahcheraghi [431]	Incorrect study design
Howard 2004 [432]	Incorrect population
Howell 1983[433]	Incorrect population
Hui 1996[435]	No relevant extractable outcomes
Huisman 2010 [436]	Systematic review checked for references
Hull 1979[437]	Incorrect intervention
Hull 1993[438]	Incorrect population
Hull 2015 [439]	No relevant outcomes reported
Hume 1973 [442]	Incorrect intervention
Ibrahim 2015 [444]	Systematic review checked for references
Ikesaka 2014[445]	Does not match protocol
Imberti 2009 [446]	No relevant outcomes reported
Ingelheim 1981 [111]	Intervention does not match protocol
Izadpanah 2015 [448]	Incorrect study design
Jameson 2011 [451]	Incorrect study design
Jameson 2012 [452]	Incorrect study design
Jameson 2012 [450]	Incorrect study design
Jamula 2009 [453]	Incorrect study design
Janvrin 1980 [455]	No results available
Jourdan 1984[459]	Incorrect population
JPRN 2009 [957]	Incorrect study design
Jprn 2013 [959]	No results available
Junqueira 2012 [460]	Incorrect population
Kahn 2012 [465]	Abstract
Kahn 2014 [464]	Incorrect population
Kakkar 1985[469]	Incorrect population

Reference	Reason for exclusion
Kakkar 1989[470]	Incorrect population
Kakkar 2014 [466]	Incorrect population
Kakkos 2012 [471]	Systematic review checked for references
Kang 2014 [473]	Incorrect population
Kawaji 2012 [479]	Incorrect study design
Kessler 2011 [482]	Incorrect comparison
Kettunen 1974[483]	Not in English
Khokhar 2013 [485]	Systematic review checked for references
Khorana 2015 [486]	Insufficient data provided for inclusion
Kierkegaard 1993[487]	Incorrect intervention
Kiil 1978A[488]	Not in English
Kill 1978B[489]	Incorrect population
Kill 1978C[490]	No relevant outcomes reported
Kill 1978D [491]	Systematic review checked for references
Kill 1978E[492]	Incorrect population
Killewich 1997[493]	Length of follow up does not match protocol
Kim 2016[494]	Incorrect intervention
Kiudelis 2010 [496]	No relevant outcomes reported
Klerk 2005 [497]	Intervention does not match protocol
Knudson 1992[500]	Incorrect study design
Koo 2014 [501]	No relevant outcomes reported
Koppenhagen 1982[504]	Incorrect population
Koppenhagen 1990[505]	Incorrect study design
Koppenhagen 1992[503]	Incorrect study design
Kosir 1998[506]	Not in English
Kourlaba 2015 [507]	Incorrect study design
Krasinski 2014 [508]	Incorrect study design
Krauss 1994[509]	Not in English
Kraytman 1976[510]	Not in English
Kraytman 1977[518]	Incorrect population
Kruse-Blinkenberg 1980[512]	Systematic review checked for references
Kujath 2013 [516]	Not in English
Kutnowski 1977[518]	Incorrect population
Kwok 2013 [519]	Systematic review checked for references
Lahnborg 1976[521]	Incorrect population
Laporte 2014 [524]	Incorrect population
Lassen 1988 [530]	Incorrect intervention
Lassen 1989 [531]	Incorrect intervention
Lenssen 2008 [549]	Incorrect population
Lassen 2012 [533]	Incorrect intervention
Lavitola 2010 [537]	Incorrect population
Lawrence 1977[538]	Incorrect population
Lawton 2017 [539]	Incorrect study design

Reference	Reason for exclusion
Le Gagneux 1987[540]	Incorrect intervention
Lebeau 1994 [542]	Does not match guideline condition
Lecumberri 2012 [545]	Incorrect population
Lecumberri 2013 [545]	Does not match guideline condition
Legnani 1990[547]	Incorrect population
Lenssen 2008 [549]	No relevant outcomes reported
Levine 1996[550]	Incorrect intervention
Levitan 2014 [552]	Incorrect study design
Li 2014 [555]	Incorrect intervention
Li 2015 [553]	Incorrect intervention
Lieberman 1994[557]	No relevant outcomes reported
Lieberman 2013 [558]	Incorrect study design
Liew 2016 [560]	Systematic review checked for references
Lim 2016 [561]	No relevant outcomes reported
Limmer 1994[562]	Incorrect population
Lin 2016 [563]	Systematic review checked for references
Lindqvist 2011 [564]	Incorrect study design
Lip 2015 [568]	Incorrect population
Liu 2014 [569]	Incorrect comparison
Lobastov 2014 [572]	Incorrect study design
Loew 1974[575]	Systematic review checked for references
Loew 1977[574]	Systematic review checked for references
Loew 1981[583]	Incorrect study design
Loffredo 2013 [576]	Systematic review checked for references
Loke 2010 [577]	Systematic review checked for references
Lou 2017 [578]	Not in English
Louis 2014 [579]	Incorrect study design
Lowe 1979[582]	Incorrect population
Lowe 1981 [583]	Incorrect study design
Lu 2009 [584]	Incorrect study design
Lubenow 2010 [585]	No relevant outcomes reported
Lyman 2015 [589]	Incorrect study design
Ma 2015 [592]	Systematic review checked for references
Macatangay 2008 [593]	No relevant outcomes reported
Macbeth 2016 [594]	Does not match guideline condition
Macoviak 1984 [598]	No relevant outcomes reported
MacCallum 1990[595]	Incorrect study design
MacIntyre 1974[597]	Incorrect population
Maniscalco 2014 [602]	Systematic review checked for references
Manns 2014 [603]	Incorrect study design
Maraveyas 2010 [607]	Incorrect intervention
Maraveyas 2012 [608]	Does not match guideline condition
Marcy 2015 [611]	Systematic review checked for references

Reference	Reason for exclusion
Marchetti 1983[610]	Incorrect study design
Mariani 2011 [612]	Incorrect population
Maurer 1997 [613]	Does not match guideline condition
McBride 1975 [618]	Incorrect intervention
McKenna 1980 [624]	Incorrect intervention
McLean 2010 [625]	Incorrect study design
Medical Research Council 1972[276]	Incorrect population
Mega 2009 [629]	Incorrect population
Melillo 2010 [631]	Systematic review checked for references
Mellbring 1986[632]	Incorrect population
Melon 1991[633]	Abstract only
Messori 2014 [634]	Incorrect population
Metzger 2015 [635]	Systematic review checked for references
Michot 2002 [637]	Incorrect intervention
Mihaljevic 2016 [639]	No relevant outcomes reported
Mirhosseini 2013 [642]	Incorrect population
Mismetti 2001[645]	Intervention does not match protocol
Mismetti 2004 [646]	Systematic review checked for references
Mitchell 2003 [647]	Incorrect population
Monreal 1995 [652]	Incorrect population
Morris 1977[655]	No relevant extractable outcomes
Morris 2010 [656]	Incorrect population
Mozafar 2013 [658]	No relevant outcomes reported
Muir 2008 [660]	Incorrect study design
Murugesan 2010 [661]	No relevant outcomes reported
Myhre 1969[662]	Non-English study
Naccarato 2010 [663]	Systematic review checked for references
Nakase 2009 [664]	Incorrect study design
National Horizon Scanning Centre (NHSC) 2008 [672]	Incorrect study design
National Horizon Scanning Centre 2010 [671]	Incorrect study design
National Institute of Health and Clinical Excellence 2009 [677]	Incorrect study design
NICE Guidance 2008 [675]	Incorrect study design
Nicolaides 1972[686]	Incorrect study design
NIHR 2014 [690]	Incorrect intervention
NIHR 2015 [248]	Incorrect study design
NIHR H.S.C. 2013 [689]	Incorrect study design
Ning 2016 [691]	Systematic review checked for references
Nurmohamed 1995[703]	Incorrect population
Nurmohamed 1996[702]	Incorrect population
Obi 2015 [706]	No relevant outcomes reported
Obolenskiy 2014 [707]	Incorrect population

Reference	Reason for exclusion
Okoye 2014 [709]	Incorrect study design
Orken 2009 [716]	No relevant outcomes reported
O'Sullivan 1972[705]	Systematic review checked for references
Overcash 2015 [717]	Incorrect study design
Ozler 2015 [719]	Incorrect population
Paciaroni 2008 [720]	Systematic review checked for references
Palareti 1996 [723]	Intervention does not match protocol
Parodi 1973[731]	Systematic review checked for references
Patel 2010 [733]	Incorrect study design
Patel 2013 [734]	Incorrect study design
Pathak 2015[735]	Intervention and comparison does not match protocol.
Pathak 2015 [736]	Systematic review checked for references
Pavon 2015 [737]	Systematic review checked for references
Pebanco 2013 [738]	Systematic review checked for references
Pengo 2016 [740]	Incorrect study design
Perka 2011 [741]	Incorrect study design
Pettila 1999[742]	Incorrect population
Pezzouli 1989[744]	Incorrect population
Pezzouli 1990[743]	Systematic review checked for references
Phan 2014 [745]	Systematic review checked for references
Phelan 2012 [746]	Incorrect population
Phung 2011 [748]	Systematic review checked for references
Pince 1981[750]	Unobtainable thesis
Pineo 2012 [751]	Incorrect population
Pinto 1970[752]	Incorrect population
Pitt 1980 [755]	Incorrect intervention
Pitto 2007 [756]	Incorrect study design
Planes 1988[759]	Incorrect study design
Plante 1979[760]	Incorrect study design
Plitt 2014 [761]	Incorrect study design
Ploumis 2009 [762]	Systematic review checked for references
Pohar 2008 [763]	Incorrect study design
Poller 1987[764]	Incorrect study design
Poller 1995[765]	Systematic review checked for references
Poulsen 2012 [767]	Incorrect study design
Poultsides 2011 [768]	Systematic review checked for references
Pour 2013 [769]	Systematic review checked for references
Powers 1989 [770]	Incorrect intervention
Prandoni 2012 [772]	Systematic review checked for references
Prins 2014 [775]	Incorrect study design
Prins 2014 [774]	Incorrect study design
Qaseem 2011 [777]	Systematic review checked for references
Qushmaq [779]	Incorrect study design

Reference	Reason for exclusion
Rachidi 2013 [780]	Incorrect study design
Rada 2013 [781]	Incorrect population
Rahn 2011 [782]	Systematic review checked for references
Rai 1997[783]	Incorrect population
Rajaskhar 2011[784]	Incorrect intervention
Rokito 1996 [817]	No relevant outcomes reported
Ramos 1996[787]	Duration of study does not match protocol
Ramos 2008 [785]	Systematic review checked for references
Raskob 2012 [788]	Systematic review checked for references
Raskob 2016 [789]	Incorrect study design
Rasmussen 2009 [466]	Systematic review checked for references
Rasmussen 2009 [790]	Systematic review checked for references
Reilmann 1989[795]	Incorrect intervention
Re-mobilize Writing Committee [791]	Incorrect population
RE-MOBILIZE Writing Committee 2009 [792]	Systematic review checked for references
Renny 1976[796]	Incorrect study design
Ribaudo 1975A[799]	Incorrect comparison
Ribaudo 1975B[798]	Incorrect comparison
Ribic 2009 [800]	Systematic review checked for references
Riemsma 2011 [801]	Incorrect study design
Riess 2009 [802]	Incorrect comparison
Riordan 2008[804]	Conference abstract
Ritzenthaler 2015 [688]	Incorrect intervention
Riva 2014 [805]	No relevant outcomes reported
Roark 2010 [807]	Incorrect study design
Robertson 2013 [809]	Systematic review checked for references
Robertson 2014 [808]	Incorrect population
Robinson 2010 [811]	No relevant outcomes reported
Robinson 2013 [810]	Incorrect comparison
Roderick 2005 [813]	Systematic review checked for references
Rodger 2012 [816]	Incorrect population
Rodger 2014 [814]	Incorrect population
Rodger 2015 [815]	Incorrect study design
Rokito 1996[817]	Incorrect study design
Romera-Villegas 2008 [818]	Incorrect population
Rondelli 2013 [819]	Systematic review checked for references
Rondina 2011[820]	Incorrect study design
Rosenberg 2011 [822]	Incorrect study design
Rosencher 2012 [823]	Incorrect study design
Rosengarten 1971[824]	Systematic review checked for references
Roth 1995 [825]	Not in English
Rothberg 2012 [826]	Incorrect study design

Reference	Reason for exclusion
Russell 2013 [830]	Systematic review checked for references
Ryan 2002 [832]	Incorrect intervention
Sachedva 2014 [834]	Systematic review checked for references
Saeed 2011 [835]	Incorrect study design
Sagar 1974[836]	Systematic review checked for references
Sagar 1975[837]	Incorrect population
Saigal 2015 [838]	Systematic review checked for references
Sajid 2012 [839]	Systematic review checked for references
Salcuni 1988[840]	Incorrect study design
Saleh 2013 [841]	Incorrect population
Salmaggi 2013 [842]	Systematic review checked for references
Salvo 2014 [843]	Incorrect study design
Samama 1988[846]	Does not match guideline condition
Sandercock 2008 [848]	Incorrect study design
Sant'Anna 2015 [849]	Incorrect intervention
Santoro 2009 [851]	Incorrect study design
Saraiya 2009 [853]	Incorrect study design
Sasahara 1984[856]	Incorrect study design
Sasahara 1986[857]	Incorrect population
Sasaki 2009 [858]	No relevant outcomes reported
Sasaki 2011 [859]	Incorrect study design
Sautter 1983 [860]	Incorrect intervention
Schiele 2010 [862]	Incorrect study design
Schmitz Huebner 1984[863]	Incorrect study design
Schreiber 1979[867]	Non-English study
Schulman 2011 [869]	Incorrect study design
Schulman 2012 [868]	Incorrect intervention
Schulman 2015 [870]	Incorrect population
Scott 2008 [872]	Incorrect study design
Scurr 1977[874]	Incorrect population
Scurr 1987[873]	Systematic review checked for references
Sharma 2015 [877]	Not in English
Shea-Budgell 2014 [878]	Systematic review checked for references
Shelkrot 2014 [881]	Systematic review checked for references
Shirai 1985[883]	Incorrect study design
Shorr 2008 [885]	Systematic review checked for references
Shosha 2017 [886]	Does not meet guideline condition
Shukla 2008 [887]	No relevant outcomes reported
Sideras 2006 [889]	Incorrect study design
Simard 2013 [891]	Incorrect study design
Simes 2014 [892]	Incorrect population
Simonetti 2014 [893]	Incorrect intervention
Singh 2012 [895]	Abstract only

Reference	Reason for exclusion
Singh 2013 [894]	Systematic review checked for references
Siragusa 1994 [896]	Conference abstract only
Sjalander 2008 [897]	Systematic review checked for references
Skeith 2012 [898]	Incorrect study design
Skillman 1978[899]	Incorrect population
Slawson 2015 [900]	Incorrect study design
Smith 2011 [901]	Systematic review checked for references
Snook 1981[902]	Incorrect interventions
Snowden 2011 [903]	Systematic review checked for references
Sobieraj 2012 [907]	Systematic review checked for references
Sobieraj 2012 [906]	Incorrect study design
Sobieraj 2013 [905]	Systematic review checked for references
Sobieraj-Teague 2011 [904]	Incorrect population
Soreff 1975 [909]	Incorrect intervention
Sourmelis 1995 [910]	Abstract only
Spencer 2014 [912]	Systematic review checked for references
Stannard 1996 [915]	Incorrect intervention
Stannard 2001[916]	Incorrect population
Stashenko 2009 [917]	Incorrect study design
Stevens 2010 [920]	Incorrect study design
Stevenson 2009 [921]	Incorrect study design
Stephenson 2016[918]	Does not match guideline condition (anti-Xa levels only)
Stewart 2013 [922]	Systematic review checked for references
Stone 1996 [923]	No relevant extractable outcomes
Stranks 1992 [924]	No relevant extractable outcomes
Sultan 2011 [928]	Abstract only
Summers 2015 [929]	Incorrect study design
Sun 2014 [930]	Systematic review checked for references
Tardy 2003 [932]	Incorrect study design
Ten Cate-Hoek 2010 [933]	Incorrect study design
Testroote 2014 [935]	Systematic review checked for references
Tetri 2008 [936]	Incorrect study design
Thourani 2013 [938]	Incorrect study design
Tomita 2008 [939]	No relevant outcomes reported
Törngren 1980[942]	Incorrect population
Traby 2010 [943]	No relevant outcomes reported
Trukulja 2010 [944]	Incorrect population
Tsutsumi 2012 [945]	Incorrect study design
Turpie 1977[949]	Incorrect population
Turpie 1979[947]	Incorrect study design
Turpie 1989[951]	Incorrect population
Turpie 2005[948]	Incorrect intervention
Turpie 2012 [953]	Incorrect study design

Reference	Reason for exclusion
Turpie 2013 [955]	Incorrect population
Turpie 2014 [950]	Incorrect study design
Uchino 2012 [960]	No relevant outcomes reported
Valle 1998[961]	Incorrect population
Van 2014 [965]	Incorrect population
van Doormaal 2011 [964]	Does not match guideline condition
Van Geloven 1977[967]	Incorrect population
Vanassche 2015 [968]	Systematic review checked for references
Vardi 2012 [969]	Systematic review checked for references
Vedovati 2014 [971]	Incorrect population
Vedovati 2015 [972]	Incorrect population
Velmahos 2005[973]	Incorrect intervention
Venous Thrombosis Clinical Study Group 1975B[974]	Incorrect study design
Veradi 1989[975]	Incorrect interventions
Verdecchia 2014 [976]	Incorrect population
Verdecchia 2015 [977]	Incorrect study design
Verso 2010 [978]	Incorrect interventions
Villa 2013 [979]	Systematic review checked for references
Voigt 1986[980]	Incorrect population
Vollans 2015 [981]	Incorrect study design
Wade 2015 [985]	HTA checked for references
Wade 2017 [984]	HTA checked for references
Wang 2016 [987]	Incorrect population
Ward 1998[989]	Incorrect intervention
Ward 2014 [990]	Incorrect study design
Warlow 1973 [991]	Incorrect population
Warlow 1973 [991]	Incorrect population
Wasserlauf 2013 [997]	Systematic review checked for references
Weber 2007 [999]	Incorrect study design
Weiss 1977[1001]	No relevant outcomes reported
Weitz 1986[1002]	No relevant outcomes reported
Welin-Berger 1982 [1003]	Incorrect intervention
Welti 1981[1005]	Not in English
Westrich 2006[1006]	Incorrect intervention
Wilkieson 2011 [1009]	No relevant outcomes reported
Willett 2013 [1011]	Systematic review checked for references
Williams 1978[1013]	No relevant outcomes reported
Williams 1988[1012]	Not in English
Windisch 2011 [1015]	No relevant outcomes reported
Wood 1973 [1021]	Incorrect intervention
Woolson 1991 [1022]	Incorrect intervention
Wu 1977[1024]	Incorrect study design

Reference	Reason for exclusion
Wu 2015 [1023]	Incorrect population
Xiao-ying 2011 [556]	Incorrect study design
Yanar 2007[1026]	Conference abstract
Yeo 2015 [1028]	Systematic review checked for references
Yi 2014 [456]	Incorrect population
Yoo 1997 [1030]	Incorrect intervention
Yoo 2016 [1029]	Incorrect population
Yoshida 2011 [35]	Incorrect study design
Yoshida 2013 [1031]	Systematic review checked for references
Young 2009 [1032]	Incorrect intervention
Yusen 2013 [1034]	Incorrect study design
Zacharski 1984 [1036]	Does not match guideline condition
Zacharski 1981 [1035]	Does not match guideline condition
Zaghiyan 2016[1037]	Incorrect intervention
Zareba 2014 [1040]	Systematic review checked for references
Zekert 1982 [1041]	Incorrect intervention
Zhang 2011 [1042]	No relevant outcomes reported
Zhao 2014 [1043]	Systematic review checked for references
Zheng 2016 [1044]	Intervention does not match protocol
Zhou 2013 [1047]	Abstract only – insufficient data
Ziemski 1979[1049]	Not in English
Zufferey 2003 [1053]	Systematic review checked for references
Zwicker 2013 [1054]	No relevant outcomes reported

Appendix O: Excluded health economic studies

O.1 Risk assessment for people admitted to hospital

O.1.1 Patients admitted to hospital

No studies were excluded.

O.1.2 Hospital admissions

No studies were excluded.

O.1.3 Risk assessment tools in patients admitted to hospital

No studies were excluded.

O.2 Risk assessment for people having day procedures

O.2.1 VTE day procedures

No studies were included.

O.2.2 Major bleeding day procedures

No studies were excluded.

O.2.3 Risk assessment tools in patients who are having day procedures (including surgery and chemotherapy) at hospital

No studies were excluded.

O.3 Reassessment

O.3.1 Reassessment of people who are admitted to hospital

No studies were excluded.

O.3.2 Reassessment of people who are having day procedures at hospital

No studies were excluded.

O.4 Risk assessment for pregnant women and women up to 6 weeks postpartum

No studies were excluded.

O.5 Giving information to patients and planning for discharge

No studies were excluded.

O.6 General VTE prevention for everyone in hospital

No studies were excluded.

O.7 Nursing care: Early mobilisation and hydration

No studies were excluded.

O.8 Obesity

No studies were excluded.

O.9 People using antiplatelets

No studies were excluded.

O.10 People using anticoagulation therapy

No studies were excluded.

O.11 Acute coronary syndromes

No studies were excluded.

O.12 Acute stroke patients

No studies were excluded.

O.13 Acutely ill medical patients

No studies were excluded.

O.14 Cancer

No studies were excluded.

O.15 Patients with central venous catheters

No studies were excluded.

O.16 Palliative care

No studies were excluded.

O.17 Critical care

No studies were excluded.

O.18 Pregnant women and women up to 6 weeks postpartum

No studies were excluded.

O.19 People with psychiatric illness

No studies were excluded.

O.20 Anaesthesia

No studies were excluded.

O.21 Lower limb immobilisation

No studies were excluded.

O.22 Fragility fractures of the pelvis, hip and proximal femur

Table 267: Studies excluded from the health economic review

Reference	Reason for exclusion
Capri 2010[149]	This study was assessed as not applicable. The population considered is all major orthopaedic surgery combined (HFS, THR, TKR). Uncertainty regarding the applicability of resource use and costs from Italy in 2007 to current NHS context. QALYs are not used as measure of outcome. It is not clear whether costs and outcomes were discounted and if so, at what rate. Time horizon is short and unlikely to capture all differences. Only symptomatic events are included in the analysis and HIT is not included.
Dranistaris 2009[269]	This study was assessed as partially applicable with very serious limitations. Uncertainty regarding the applicability of resource use and cost data from Canada in 2007 to current NHS context. QALYs were not used as measure of outcome. The structure of the model does not include PE, asymptomatic DVT, any of the long-term outcomes (PTS and CTEPH) or Major bleeding in the post-discharge period (even for the extended prophylaxis strategies). The time horizon is short and does not capture all likely differences in costs and outcomes. Resource use data is based on a survey of only 3 Canadian hospitals so may not be representative of all Canadian hospitals. Some of the unit costs are based on local unit costs, so may not represent National unit costs. Only one-way sensitivity analysis was undertaken. There is a potential conflict of interest.

O.23 Elective hip replacement surgery

Table 268: Studies excluded from the health economic review

Reference	Reason for exclusion
Annemans 2004[41]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was

Reference	Reason for exclusion
	developed, this study was selectively excluded.
Bischof 2006[103]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Bjorvatn and Kristiansen 2005[104]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Braidy 2011[125]	This study was assessed as not applicable. QALYs are not used as measure of outcome. The population was a mixed population including patients with AF and those treated from VTE. Uncertainty regarding the applicability of unit costs and resource use from the Australia in 2009 to current NHS context.
Capri 2010[149]	This study was assessed as not applicable. The population considered is all major orthopaedic surgery combined (HFS, THR, TKR). Uncertainty regarding the applicability of resource use and costs from Italy in 2007 to current NHS context. QALYs are not used as measure of outcome. It is not clear whether costs and outcomes were discounted and if so, at what rate. Time horizon is short and unlikely to capture all differences. Only symptomatic events are included in the analysis and HIT is not included.
Dahl and Pleil 2003[228]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Davies 2000[234]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Diamantopoulos 2010[257]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Dranitsaris 2004[267]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Dranistaris 2009[269]	This study was assessed as partially applicable with very serious limitations. Uncertainty regarding the applicability of resource use and cost data from Canada in 2007 to current NHS context. QALYs were not sued as measure of outcome. The structure of the model does not include PE, asymptomatic DVT, any of the long-term outcomes (PTS and CTEPH) or Major bleeding in the post-discharge period (even for the extended prophylaxis strategies). The time horizon is short and does not capture all likely differences in costs and outcomes. Resource use data is based on a survey of only 3 Canadian hospitals so may not be representative of all Canadian hospitals. Some of the unit costs are based on local unit costs, so may not represent National unit costs. Only one way sensitivity analysis was undertaken. The study is industry funded.
Gommez-Outes 2014[352]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Gordois 2003[354]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Haentjens 2004[374]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Hamidi 2013[381]	This study was assessed as partially applicable with potentially serious

Reference	Reason for exclusion
	limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Lundkvist 2003[587]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
McCullagh 2009[620] and McCullagh 2012[621]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
McDonald 2012[622]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Migliaccio-Walle 2012[638]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
NICE 2007 (CG46)[670]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
NCGC 2010 [CG92][666]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this was selectively excluded.
Postma 2012[766]	This study was assessed as not applicable. QALYs are not used as measure of outcome. Uncertainty regarding the applicability of unit costs and resource use from the Netherland in 2010 to current NHS context. The interventions are different from considered representative to UK standard practice, with nardoparin and dabigatran 150 mg included and prophylaxis administered for 50 days post THR and 36 days after TKR
Reeves 2004[793]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Revankar 2013[797]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Ryttberg 2011[833]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Sterne 2017[919]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
TA245 2012 & Riemsma 2011 [678,801]	This TA and accompanying ERG report were assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this was selectively excluded
TA157 2008[675]	This TA was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this was selectively excluded
TA170 2009 & Stevenson 2009 [677,921]	This TA and the accompanying ERG report was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this was selectively excluded.
Wade 2015 [985]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study has been selectively excluded.
Wolowacz, 2009[1017]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was

Reference	Reason for exclusion
	developed, this study has been selectively excluded.
Wolowacz, 2010[1018]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study has been selectively excluded.
Zindel 2012[1051]	This study was assessed as not applicable. QALYs are not used as measure of outcome. Uncertainty regarding the applicability of unit costs and resource use from Germany in 2010 to current NHS context. The time horizon is only 3 months. The results are reported from the perspective of the German statutory health insurance.

O.24 Elective knee replacement

Table 269: Studies excluded from the health economic review

Reference	Reason for exclusion
Annemans 2004[41]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Bischof 2006[103]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Bjorvatn and Kristiansen 2005[104]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Braidy [125]2011	This study was assessed as not applicable. QALYs are not used as measure of outcome. The population was a mixed population including patients with AF and those treated from VTE. Uncertainty regarding the applicability of unit costs and resource use from the Australia in 2009 to current NHS context.
Capri 2010[149]	This study was assessed as not applicable. The population considered is all major orthopaedic surgery combined (HFS, THR, TKR). Uncertainty regarding the applicability of resource use and costs from Italy in 2007 to current NHS context. QALYs are not used as measure of outcome. It is not clear whether costs and outcomes were discounted and if so, at what rate. Time horizon is short and unlikely to capture all differences. Only symptomatic events are included in the analysis and HIT is not included.
Diamantopoulos 2010[257]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Dranitsaris 2004[267]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Dranistaris 2009[269]]	This study was assessed as partially applicable with very serious limitations. Uncertainty regarding the applicability of resource use and cost data from Canada in 2007 to current NHS context. QALYs were not sued as measure of outcome. The structure of the model does not include PE, asymptomatic DVT, any of the long-term outcomes (PTS and CTEPH) or Major bleeding in the post-discharge period (even for the extended prophylaxis strategies). The time horizon is short and does not capture all likely differences in costs and outcomes. Resource use data is based on a survey of only 3 Canadian hospitals so may not be representative of all Canadian hospitals. Some of the unit costs are based on local unit costs, so may not represent National unit costs. Only one way sensitivity

Reference	Reason for exclusion
	analysis was undertaken. The study is industry funded.
Gommez-Outes 2014[352]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Gordois 2003[354]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Haentjens 2004[374]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Hamidi 2013[381]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Lundkvist 2003[587]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
McCullagh 2012[621]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
McDonald 2012[622]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Migliaccio-Walle 2012[638]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
NICE 2007 (CG46)[670]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
NCGC 2010 [CG92][666]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this was selectively excluded.
Postma 2012[766]	This study was assessed as not applicable. QALYs are not used as measure of outcome. Uncertainty regarding the applicability of unit costs and resource use from the Netherland in 2010 to current NHS context. The interventions are different from considered representative to UK standard practice, with nardoparin and dabigatran 150 mg included and prophylaxis administered for 50 days post THR and 36 days after TKR
Reeves 2004[793]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Revankar 2013[797]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Ryttberg 2011[833]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
Sterne 2017[919]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study was selectively excluded.
TA245 2012 & Riemsma 2011 [678 ,801]	This TA and accompanying ERG report were assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this was selectively excluded

Reference	Reason for exclusion
TA157 2008[675]	This TA was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this was selectively excluded
TA170 2009 & Stevenson 2009 [677 ,921]	This TA and the accompanying ERG report were assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this was selectively excluded.
Wade 2015 [985]	This study was assessed as directly applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study has been selectively excluded.
Wolowacz, 2009[1017]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study has been selectively excluded.
Wolowacz, 2010[1018]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was developed, this study has been selectively excluded.
Zindel 2012[1051]	This study was assessed as not applicable. QALYs are not used as measure of outcome. Uncertainty regarding the applicability of unit costs and resource use from Germany in 2010 to current NHS context. The time horizon is only 3months. The results are reported from the perspective of the German statutory health insurance.

O.25 Non-arthroplasty orthopaedic knee surgery

No studies were excluded.

O.26 Foot and ankle orthopaedic surgery

No studies were excluded..

O.27 Upper limb orthopaedic surgery

No studies were excluded.

O.28 Spinal surgery

No studies were excluded.

O.29 Cranial surgery

No studies were excluded.

O.30 Spinal injury

No studies were excluded.

O.31 Major trauma

No studies were excluded.

O.32 Abdominal surgery (excluding bariatric surgery)

Table 270: Studies excluded from the health economic review

Reference	Reason for exclusion
Morimoto 2014[654]	This study was assessed as partially applicable with very serious limitations. Uncertainty regarding the applicability of unit costs and prophylaxis regimens used in Japan to current NHS context. QALYs were not used as an outcome. The prophylaxis regimens described in the paper are not standard practice in the NHS. The analysis is based on data collected retrospectively and comparison with hypothetical scenarios. The health states considered in the analysis do not include any long term outcomes such as CTEPH and PTS. The interventions examined were assumed to have 100% efficacy, with no supporting evidence. The sources of the unit costs, the currency year and the perspective of the analysis are not described. No sensitivity analysis has been undertaken.
National Collaborating Centre for Acute Care 2007[670]	This was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was available, [666] this study was selectively excluded.
Gozzard 2004[357]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was available, [666] this study was selectively excluded.
Reeves 2004[793]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was available, [666] this study was selectively excluded.

O.33 Bariatric surgery

No studies were excluded.

O.34 Cardiac surgery

No studies were excluded.

O.35 Thoracic surgery

No studies were excluded.

O.36 Vascular surgery

No studies were excluded.

O.37 Head and neck surgery

O.37.1 Oral and maxillofacial surgery

No studies were excluded.

O.37.2 Ear, nose and throat (ENT) surgery

No studies were excluded.

Appendix P: Cost-effectiveness analysis: Prophylaxis strategies for people undergoing elective total hip and elective total knee replacement surgeries

P.1 Introduction

Thrombo-prophylaxis for people admitted to hospital for elective total hip replacement (eTHR) and those admitted for elective total knee replacement (eTKR) has been prioritised for economic modelling. The guideline committee considered the decision to offer prophylaxis for these populations and the choice of the prophylaxis strategy to have substantial economic impact; given the large size of these populations. According to the national joint registry 13th report, in 2015; there were 84,462 hip replacement operations and 94,437 knee replacement operations.[109] The large majority of these operations are elective primary total joint replacement procedures. Hence, the following two review questions were prioritised by the committee for economic modelling:

1. What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective hip replacement?

2. What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective knee replacement?

For the eTHR population, 32 economic studies, in 35 publications, relating to this review question were identified but were excluded due limited applicability, methodological limitations, a combination of limited applicability and methodological limitations or the availability of more applicable evidence.[41 ,103 ,104 ,125 ,149 ,228 ,234 ,257 ,267 ,269 ,352 ,354 ,374 ,381 ,587 ,620-622 ,638 ,666 ,670 ,675 ,677 ,678 ,766 ,793 ,797 ,801 ,833 ,919 ,921 ,985 ,1017 ,1018 ,1051] These included 3 NICE TAs, 2 evidence review group [ERG] reports and the CG92 model for standard duration and post discharge prophylaxis. Also, 10 of these publications were previously included in CG46.[41 ,103 ,104 ,228 ,234 ,267 ,354 ,374 ,587 ,793]

Similarly, for the eTKR population, 30 economic studies, in 32 publications, relating to this review question were identified but were excluded due limited applicability, methodological limitations, a combination of limited applicability and methodological limitations or the availability of more applicable evidence.[41 ,103 ,104 ,125 ,149 ,257 ,267 ,269 ,352 ,354 ,374 ,381 ,587 ,621 ,622 ,638 ,666 ,670 ,675 ,677 ,678 ,766 ,793 ,797 ,801 ,833 ,919 ,921 ,985 ,1017 ,1018 ,1051] These included the same 3 NICE TAs, 2 evidence review group [ERG] reports and the CG92 model for standard duration and post discharge prophylaxis.

The results of these economic evaluations supported the cost effectiveness of prophylaxis compared to no prophylaxis. The choice of the most cost-effective prophylaxis strategy, however, varied among these studies. Hence; the guideline committee prioritised this area for economic modelling to assess the cost effectiveness of VTE prophylaxis strategies in eTHR and eTKR populations in England.

Methods

P.1.1 Model overview

A cost-utility analysis was undertaken to evaluate the cost effectiveness of the different thrombo-prophylaxis options for people undergoing elective hip or elective knee replacement. A two-stage modelling approach was used, where a decision tree was used to represent the acute phase (up to

90- days post-operatively) and a Markov Chain cohort model was used to represent the long-term (from 90 days post operatively up to lifetime time horizon). The model is used to calculate the lifetime quality-adjusted life years (QALYs) and costs accumulated when using each of the prophylaxis strategies. The analysis was conducted from a UK NHS and personal social services (PSS) perspective, in accordance with the NICE reference case, for interventions with a health focus[673].

P.1.1.1 Population

In line with the clinical review; the model covers two distinct populations: Adults and young people (16 years and over) admitted for eTHR and those admitted for eTKR. These populations were modelled separately due to the differences in their risk of VTE and cohort characteristics. None of the pre-specified subgroups in the clinical review protocol were considered for modelling as the results of the clinical review did not show any heterogeneity to warrant separate analysis.

P.1.1.2 Comparators

The comparators for each population were selected based on the availability of evidence from the clinical review, direct and network meta-analyses (N)MAs and discussion with the guideline committee around which regimens are considered to be relevant to current clinical practice in the UK.

The committee considered LMWHs to be interchangeable; based on a class effect. High and low doses of the pharmacological prophylaxis options were not included in the model; while both standard and extended durations were included. Other comparators in the clinical review that were not included in the model were those that the committee did not consider to be routinely used in current practice in the UK (for example Vit K antagonists (VKAs) and routine use of unfractionated heparin (UFH). Interventions included in the model are outlined in **Table 271** below. Some interventions were not possible to include in the model as they could not be included in the NMAs; as they were not connected to the DVT and PE networks; are listed in **Table 272** below.

Table 271: Interventions included in the model by population

	Elective Total Hip Replacement (eTHR)	Elective Total Knee Replacement (eTKR)
None	No prophylaxis	No prophylaxis
Mechanical only	AES (above-knee) AES (length unspecified)	AES (length unspecified)
	IPCD (length unspecified)	IPCD (length unspecified)
	Foot pump	Foot pump
	Foot pump + AES	Foot pump + AES
Pharmacological Only	LMWH (standard dose; standard duration)	LMWH (standard dose; standard duration)
	LMWH (standard dose; extended duration)	LMWH (standard dose; extended duration)
	Dabigatran	Dabigatran
	Rivaroxaban	Rivaroxaban
	Apixaban	Apixaban
	Aspirin (standard duration)	Aspirin (standard duration)
	LMWH (standard dose, standard duration) followed by aspirin (extended duration)	
Combination-	LMWH (standard dose; standard	LMWH (standard dose; standard

	Elective Total Hip Replacement (eTHR)	Elective Total Knee Replacement (eTKR)
(Pharmacological + mechanical)	duration) + AES	duration) + AES
	LMWH (standard dose; extended duration) + AES	Fondaparinux + AES
	Fondaparinux + AES	

Abbreviations: AES: anti-embolism stockings; eTHR: elective total hip replacement; eTKR: elective total knee replacement; IPCD: intermittent pneumatic compressions device; LMWH:low molecular weight heparin.

Table 272: Interventions not included in the NMAs and the model by population

	Elective Total Hip Replacement (eTHR)	Elective Total Knee Replacement (eTKR)
Mechanical	IPCD + AEs	-
Combination	LMWH (standard dose; standard duration) + IPCD+ AES	Fondaparinux + IPCD + AEs
	Fondaparinux + IPCD+ AES	
	Fondaparinux + IPCD	

Abbreviations: AES: anti-embolism stockings; eTHR: elective total hip replacement; eTKR: elective total knee replacement; IPCD: intermittent pneumatic compressions device; LMWH:low molecular weight heparin.

P.1.1.3 Time horizon, perspective, discount rates used

The analysis follows the standard assumptions of the reference case including discounting at 3.5% for costs and health effects, and incremental analysis is conducted. A sensitivity analysis using a discount rate of 1.5% for costs and health effects was also conducted. Lifetime time horizon was used.

P.1.2 Approach to modelling

We followed a two-stage modelling approach. A decision tree was used to model the acute phase (surgery to 90 days post-operatively) and a Markov Chain was used to model the long-term events beyond 90 days post-operatively. The relative efficacy of the included comparators on the model outcomes was applied during the acute phase of the model, after which progression through the model was treatment-independent and based on epidemiological data for mortality, the incidence of post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). Uncertainty was explored through probabilistic analysis and one-way sensitivity analyses.

A number of assumptions were made when developing the model. These have been discussed in detail with and agreed by the committee. The key assumptions are outlined below but are also discussed in more detail in subsequent sections of this report:

Assumptions:

1- Asymptomatic DVT is not diagnosed in practice and will not be treated or lead to extra costs or loss in quality of life in the short term.
2- Only one symptomatic event is allowed in the model in the first 90 days; given that the treatment course for these events is 3 months long and once an event is diagnosed; the individual would receive treatments and would no longer be considered to be receiving primary prophylaxis.

3- Those who develop symptomatic proximal DVT or PE will receive treatment. The treatment used was assumed to be either a direct oral anticoagulant (rivaroxaban or apixaban) or LMWH followed by vit-K antagonist (warfarin) in a ratio of 50% each.
4- It was assumed the treatment of VTE events is 100% effective, regardless of which VTE treatment regimen is used and no allowance for recurrence was made in the model. This was decided based on discussions with the committee where it was decided that the rate of recurrence after a provoked VTE is much lower compared to unprovoked VTE event. It was also felt that the prevention of a provoked event will not necessarily lead to prevention of recurrence which might be a result of a previous undiagnosed VTE event or an inherent susceptibility, including thrombophilia.

P.1.2.1 Model structure

A separate model is run for each of the two populations: eTHR and eTKR. This was decided to reflect the difference in baseline VTE and bleeding risks, treatment duration and the characteristics of the target population. However, the structure of the model is the same for both populations. The model consists of a simple decision tree covering the acute phase from admission up to 90 days post-operatively, to cover the period included in the definition of hospital-acquired VTE, followed by a Markov chain for the remaining model time horizon (lifetime in the base case). The structure is repeated for each prophylaxis strategy.

The decision tree consists of the clinical events: DVT (symptomatic proximal, symptomatic distal, asymptomatic proximal and asymptomatic distal), non-fatal PE, fatal PE, Surgical site bleeding, non-surgical site bleeding (gastrointestinal (GI) bleeding, intracranial haemorrhage (ICH)/haemorrhagic stroke, other major bleeding), fatal major bleeding (MB), clinically-relevant non-major bleeding (CRNMB) and heparin-induced thrombocytopaenia (HIT).

Of the VTE events; symptomatic proximal DVT and PE were assumed to always require treatment. Symptomatic distal DVT was assumed to require treatment in 50% of cases. Treatment of DVT and PE was assumed to continue for 3 months, given the provoked nature of the event, and be either a therapeutic dose of an oral anticoagulant (rivaroxaban or apixaban) or a parentral anticoagulant for 7 days + warfarin for the 3 months. Treatment with either of the two strategies was assumed to be 100% effective and recurrence was not considered. This was based on the guideline committee's expert opinion, given the low rate of recurrence following a provoked VTE event as well as the assumption that prevention of a provoked event does not automatically lead to prevention of the recurrence given that the recurrence could be secondary to any previous VTE event.

Major bleeding (MB) events in the model could be at the surgical site; in which case it would result in return to theatre, or at another site. MB occurring in the GI tract was assumed to require intervention in 13% of cases[666]. ICH/haemorrhagic stroke was assumed to lead to disability.

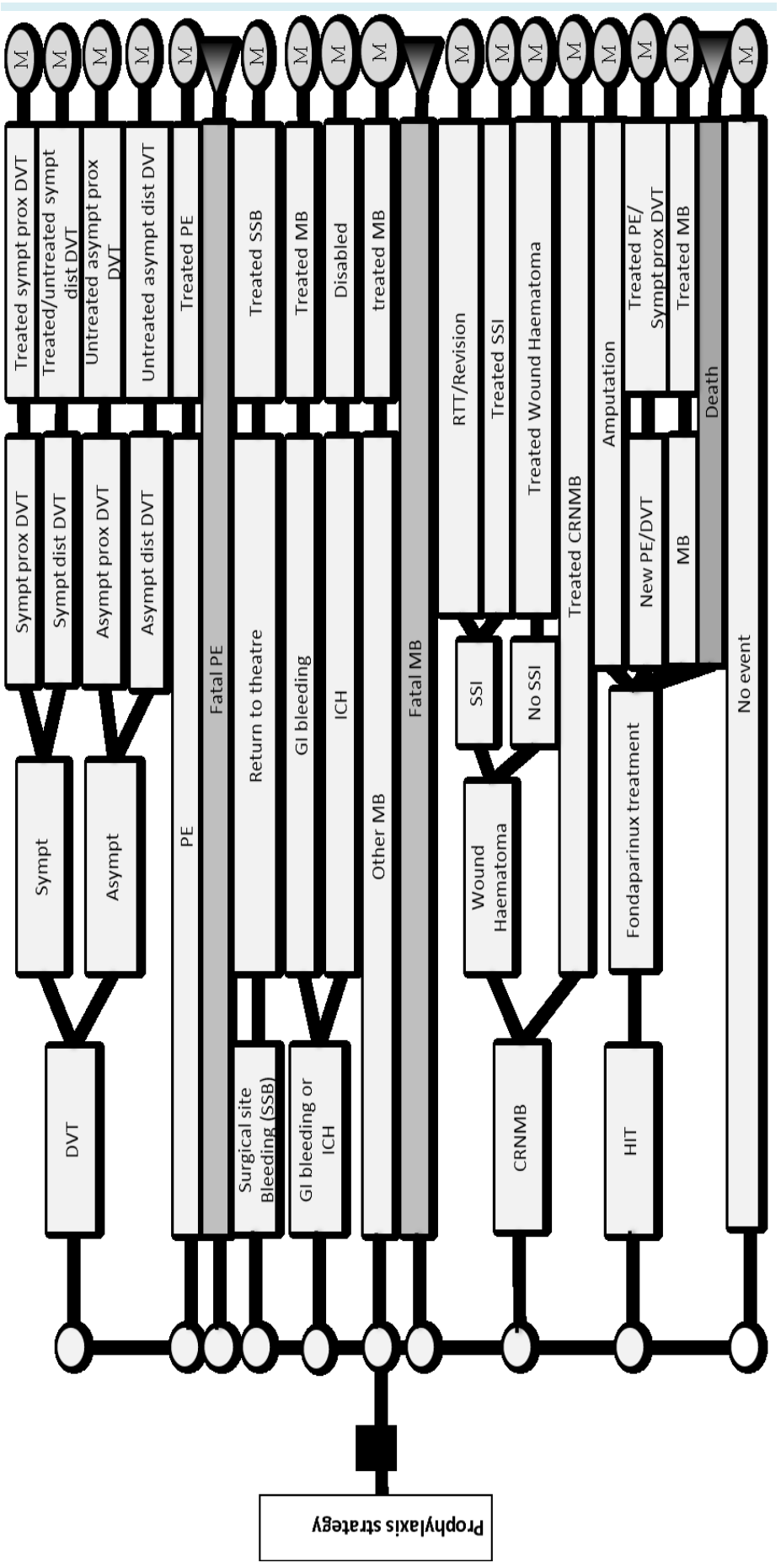
Individuals who develop CRNMB were assumed to either be treated or develop a wound haematoma that could lead to a surgical site infection (SSI). SSIs could either be medically treated or require surgical intervention; which could be either a return to theatre or a revision arthroplasty, in a ratio of 1:1.

Individuals developing HIT were assumed to be treated with a therapeutic dose of fondaparinux. The outcomes of treatment were based on data from two trials; in line with the ACCP 2012 guideline, and include successful treatment, new thrombosis (assumed to be either symptomatic proximal DVT or PE in a ratio of 1:1), major bleeding or death. The structure of the decision tree is presented in **Figure 845**.

The long-term part is represented by a Markov model. Individuals enter the model in one of the following states; based on where they end up at the end of the 90 days post-operatively: Well, post-symptomatic proximal DVT, post-symptomatic distal DVT, post-asymptomatic proximal DVT, post-

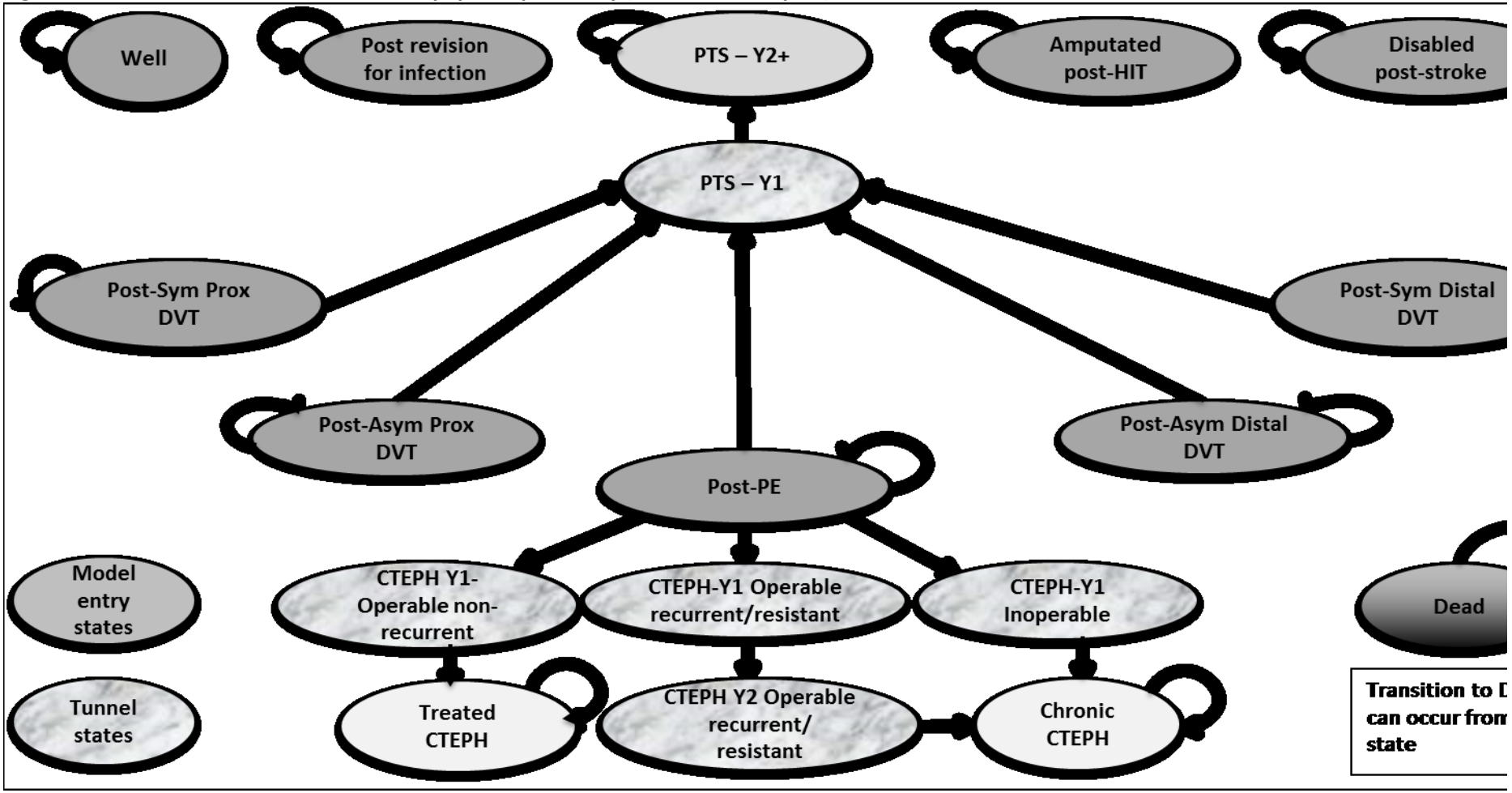
asymptomatic distal DVT, post-PE, amputated post-HIT, disabled post-stroke, post-revision for infection. In the first two years, individuals in a post-VTE state can develop post-thrombotic syndrome (PTS). Those in the post-PE state can also develop chronic thromboembolic pulmonary hypertension (CTEPH). Those with CTEPH could either undergo a pulmonary endarterectomy (PEA) and be completely cured or have a recurrence after the PEA. Those with non-operable CTEPH or refuse to have the operation were assumed to be treated with lifelong anticoagulation and targeted medical therapy. The first year after the diagnosis of each of PTS or CTEPH is represented in the model by a tunnel state. Additionally, the second year after an operable but recurrent/resistant CTEPH is also represented by a tunnel state to account for the difference in costs from a chronic CTEPH state. Transitioning to death is allowed from any state in the model, to represent all-cause mortality. The structure of the Markov cohort model is illustrated in **Figure 846.**

Figure 845: Model structure up to 90 days post-operatively (Decision tree part)



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

Figure 846: Model structure after 90 days post-operatively (Markov model part)



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

P.1.2.2 Uncertainty

The model was run probabilistically to take account of the uncertainty around the input parameters' point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 2,500 times for the base case and results were summarised.

The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a quality of life weighting will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in **Table 273** and in the relevant input summary tables in section **P.1.3.1**. Probability distributions in the analysis were parameterised using error estimates from data sources. Where these estimates were not available; the standard error was assumed to be equal to 10% of the mean value.

For the VTE and bleeding event rates which were calculated based on the NMA results, the probability distribution was constructed using the CODA for the probability or the log odds ratio of the respective event from the WinBUGs output in order to maintain the correlation between these parameters.

Table 273: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Utility	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: $Alpha = mean^2 \times [(1-mean)/SE^2] - mean$ $Beta = Alpha \times [(1-mean)/mean]$
Utility decrements	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calculated as follows: $Alpha = (mean/SE)^2$ $Beta = SE^2/Mean$

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- Drug costs
- The NHS reference costs and the mortality rates from life tables for England and Wales were not varied probabilistically as they are based on national data and therefore the level of uncertainty in the model inputs was considered to be very low and did not warrant incorporation.

In addition, deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. The sensitivity analyses that were undertaken are described in **section P.1.5**.

P.1.3 Model inputs

P.1.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic reviews undertaken during the development of the guideline, supplemented by additional data sources as required. Model inputs were validated with the clinical members of the guideline committee. A summary of the model inputs used in the base case analysis is provided in **Table 274** below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 274: Summary of base-case model inputs

Input	Data	Source
Population	Adults and young people (16 years and over) undergoing eTHR or eTKR	Guideline scope
Perspective	UK NHS and PSS	NICE reference case –Guidelines Manual[673]
Time horizon	Lifetime	NICE reference case- Guidelines Manual[673]
Discount rate	Costs and outcomes: 3.5%	NICE reference case-Guidelines Manual[673]
Cohort settings		
Start age (years)	eTHR: 68.7 (SD= 11.32) eTKR: 69.3 (SD=9.58)	National Joint Registry Annual Report 2016[109]
Male	eTHR: 40% eTKR: 44%	National Joint Registry Annual Report 2016[109]
BMI (kg/m^2)	eTHR: 28.7 eTKR: 30.9	National Joint Registry Annual Report 2016[109]
Baseline risks - e THR		
DVT (symptomatic and asymptomatic)	5.54%	Calculated based on Jameson 2011[451] and Quinlan 2007[778]
Symptomatic DVT	0.94%	Jameson 2011[451]
Proportion of symptomatic DVTs that are proximal	83.3%	Revankar 2013 [797]based on data from ADVANCE trials
Asymptomatic DVT	4.6%	Calculated based on [451] and Quinlan 2007[778]
Proportion of asymptomatic DVTs that are proximal	26.2%	Revankar 2013 Revankar, 2013 #3341} based on data from ADVANCE trials
Non-fatal PE	0.68%	Jameson 2011[451]
Mortality from PE	17% (1/6)	Randomised controlled trials in our systematic review
Major bleeding at the surgical site	2.29%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
GI and cerebrospinal bleeding	0.72%	Jameson 2011[451]
Other major bleeding	0.2%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review

Input	Data	Source
Clinically-relevant non-major bleeding (CRNMB)	2.95%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
Wound haematoma as percentage of CRNMB	22.73% (5/22)	Calculated from the LMWH randomised controlled trials in our systematic review
Heparin-induced thrombocytopenia (HIT)	0.17%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
Baseline risk - eTKR		
DVT (symptomatic and asymptomatic)	14%	Calculated based on Jameson 2012[450] and Quinlan 2007[778]
Symptomatic DVT	0.63%	Jameson 2012
Proportion of symptomatic DVTs that are proximal	20%	Revankar 2013 based on data from ADVANCE trials
Asymptomatic DVT	13.37%	Calculated based on Jameson 2012 [450] and Quinlan 2007[778]
Proportion of asymptomatic DVTs that are proximal	8.8%	Revankar 2013[797] based on data from ADVANCE trials
Non-fatal PE	0.45%	Jameson 2012 [450]
Mortality from PE	17%	assumed equal to eTHR as there were no events in the single trial of LMWH (standard dose, standard duration)+ AEs
Major bleeding at the surgical site	0.64%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
GI and cerebrospinal bleeding	0.39%	Jameson 2012 [450]
Other major bleeding	0.2%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
CRNMB	4.15%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
Wound haematoma as percentage of CRNMB	18.97% (11/58)	Calculated from the LMWH randomised controlled trials in our systematic review
HIT	0.92%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
Other parameters		
Proportion requiring return to theatre after surgical site major bleeding	100%	Standard definition of major bleeding and expert opinion

Input	Data	Source
Proportion requiring intervention after GI bleeding	13%	CG92 [666]
Surgical site infection due to haematoma	25.77% (25/97)	Wang 2014[988]
Probability of revision/return to theatre due to infection	44% (11/25)	Wang 2014[988]
Long term events		
2-year incidence of PTS after :		
Symptomatic proximal DVT	40%	Kahn 2016[463] & guideline committee Expert opinion
Symptomatic distal DVT	10%	Heit 2001 [412], Botteman 2002 [121]and guideline committee opinion
Asymptomatic proximal DVT	15%	Wille-Jorgensen 2005 [1010]
Asymptomatic distal DVT	3.75%	Heit 2001 [412], Botteman 2002 [121]
Non-fatal PE	15%	Guideline committee expert opinion
Proportion of PTS that is severe	23%	Wolowacz 2009 [1017](average from 8 incidence studies)
2-year incidence of CTEPH after non-fatal PE	3.2% (95% CI: 1.5%–3.1%)	Ende-Verhaar 2017 [287](systematic review of incidence studies)
CTEPH mortality	20%	CG92 [666]
Costs (£)		
Symptomatic proximal DVT	eTHR: £457 eTKR: £457	see section P.1.3.6.2.1
Symptomatic distal DVT	eTHR: £295 eTKR: £295	see section P.1.3.6.2.1
Non-fatal PE	eTHR: £991 eTKR: £992	see section P.1.3.6.2.1
Return to theatre for surgical site bleeding	eTHR: £6,278 eTKR: £6,177	NHS Schedule for Reference Costs 2015-2016 [250](unit cost for primary eTHR) NHS Schedule for Reference Costs 2015-2016[250] (unit cost for primary eTKR
GI bleeding with intervention	£2,409	NHS Schedule for Reference Costs 2015-2016[250]
GI bleeding without intervention	£855	NHS Schedule for Reference Costs 2015-2016[250]
Haemorrhagic Stroke		
acute event-admission	£4,354	Weighted Cost of non-elective long stay admission for stroke with CC score 0-3 to 16+. HRG codes AA35A to AA35F.NHS Schedule for Reference Costs 2015-2016[250]
Acute event- other costs for the first 90 days	£3,255	Three month costs calculated based Weighted average cost of the cost of stroke dependent state and independent state in year 1 from CG144 (VTE management and thrombophilia testing) less the cost of the

Input	Data	Source
		acute stroke admission.[668] Costs inflated to 2015-2016.
Y1 –dependent state	£29,776	CG144 (VTE management and thrombophilia testing) [668] Costs inflated to 2015-2016
Y1 –independent state	£4,971	CG144 (VTE management and thrombophilia testing) [668] Costs inflated to 2015-2016
Y2+ – dependent state	£15,108	CG144 (VTE management and thrombophilia testing) [668] Costs inflated to 2015-2016
Y2+ – independent state	£1,172	CG144 (VTE management and thrombophilia testing) [668] Costs inflated to 2015-2016
CRNMB (post-discharge)	£242	Guideline committee expert opinion (2 outpatient visits)
Surgical site infection-medically treated	£3,696	NHS Schedule for Reference Costs 2015-2016
Revision surgery for infected joint	eTHR: £19,514 eTKR: £19,203	Kallala 2015 and NHS Schedule for Reference Costs 2015-2016
HIT	£463	NHS Schedule for Reference Costs 2015-2016[250]
Amputation after HIT:		
acute event	£10,300	CG 147 (Lower Limb Peripheral Arterial Disease)[667] adjusted for inflation to 2015-2016 values
Y1	£31,259	CG 147 (Lower Limb Peripheral Arterial Disease) [667] adjusted for inflation to 2015-2016 values
Y2+	£25,987	CG 147 (Lower Limb Peripheral Arterial Disease)[667] adjusted for inflation to 2015-2016 values
PTS		
Mild/Moderate -Year 1	£841	Caprini 2003 [153] converted to 2000 GBP OECD PPP conversion and inflated to 2015-2016 values
Mild/Moderate -Year 2+	£342	Caprini 2003 converted to 2000 GBP OECD PPP)[715] conversion factor and inflated to 2015-2016 values
Severe -Year 1	£3,824	Caprini 2003 converted to 2000 GBP OECD PPP conversion)[715]and inflated to 2015-2016 values
Severe -Year 2+	£1,680	Caprini 2003 converted to 2000 GBP OECD PPP conversion)[715] and inflated to 2015-2016 values
CTEPH		
Operable-Y1	£28,671	see section P.1.3.6.3.1
Recurrent/Resistant- Y1	£29,470	see section P.1.3.6.3.1

Input	Data	Source
Inoperable-Y1	£9,677	see section P.1.3.6.3.1
Recurrent/resistant- Y2	£21,845	see section P.1.3.6.3.1
Chronic-Y2+	£13,967	see section P.1.3.6.3.1
Treated CTEPH	£147	see section P.1.3.6.3.1

Abbreviations: BMI: body mass index; CRNMB: clinically-relevant non-major bleeding; CTEPH: chronic thromboembolic pulmonary hypertension; DVT: deep vein thrombosis; eTHR: elective total hip replacement; eTKR: elective total knee replacement; GI: gastrointestinal; HIT: Heparin-induced thrombocytopenia; LMWH: low molecular weight hepari; PE: pulmonary embolism; PTS: post-thrombotic syndrome; Y1: year 1, Y2+: year 2 and beyond.

P.1.3.2 Initial cohort settings

The cohort characteristics for each of these populations were based on the data reported in the National Joint Registry (NJR) 13th annual report;[109] which were collected up to December 2015 (see **Table 275**)

Table 275: Cohort characteristics based on the National Joint Registry data for operations undertaken in 2015

	THR	TKR
Age (years) (mean)	68.7	69.3
Age (SD)	11.32	9.58
% male	40%	44%
BMI (kg/m2) (mean)	28.7	30.9

Abbreviations: BMI: body mass index; SD: standard deviation; THR: total hip replacement; TKR: total knee replacement.

P.1.3.3 Baseline risk

The baseline risk estimates for VTE and major bleeding events were based on two large observational cohort studies that used the NJR data[450,451]. In both studies, data from the NJR for England and Wales linked to an administrative database of hospital admissions in the English National Health Service (HES database) were analysed. For the THR population, a total of 108,584 patients operated on between April 2003 and September 2008 were included and followed up for 90 days.[451] Of these, 78.9% received LMWH as the pharmacological prophylaxis (n=85,642) and 72% of them had additional mechanical prophylaxis. The mechanical prophylaxis method used was assumed to be AEs, based on data from NJR for the year 2008,[794] where stockings were the most commonly prescribed mechanical prophylaxis method for THR patients (62%). LMWH was assumed to have been used in the standard dose (40 mg once daily) and duration as the study covered the procedures performed before the publication of CG92 which recommended the use of extended rather than standard duration of LMWH for this population.

For the TKR population, a total of 156,798 patients operated on over the same period were included and followed for 90 days.[450] Of these, 120,639 patients (76.9%) were prescribed LMWH as the pharmacological prophylaxis and 79.5% of them had mechanical prophylaxis. Similar to THR, and based on NJR data, stockings were the most commonly used mechanical prophylaxis method in 2008, where it was used in 66% of patients.[794]

The two studies reported the number of events for symptomatic DVT only and not all DVT which is the outcome analysed in the guideline's DVT NMAs. Hence, we used the ratio of asymptomatic to symptomatic DVT events as reported in Quinlan 2007[778] (symptomatic DVTs = 17% of all DVTs for

THR and 4.5% for TKR) to estimate the number of all DVT events that would have been observed in these studies; based on the reported number of symptomatic DVTs. The results are reported in **Table 276**. The number of DVT events and total number of patients were used to characterise a binomial distribution that was used in the NMA model for the all DVT (symptomatic and asymptomatic) outcome to allow the calculation of the relative risk and the event rate for each of the strategies included in the NMA.

Table 276: Observational study data for the total hip replacement and total knee replacement population on prophylaxis with LMWH (standard dose/standard duration) +AEs and number of all DVT events estimated based on these data

Outcome (a)	Total hip replacement (N= 85642)[451] n (%)	Total knee replacement (N= 156,798)[450] n (%)
DVT (Symptomatic)	806 (0.94%)	762 (0.63%)
PE (non-fatal)	583 (0.68%)	539 (0.45%)
MB (non-surgical site) (b)	620 (0.72%)	465 (0.39%)

Abbreviations: DVT: deep vein thrombosis; MB: major bleeding; OR: odds ratio; PE: pulmonary embolism.
(a) results of the unadjusted analysis
(b) defined as Cerebrovascular accident/gastrointestinal haemorrhage (non-fatal)

It was not possible to find an estimate of baseline risk of surgical site bleeding, other major bleeding and clinically-relevant non-major bleeding from the NJR data or published observational cohort studies of LMWH. Hence, for these outcomes, the baseline risk was calculated using a single arm meta-analysis of LMWH randomised controlled trials included in the major bleeding NMA. The meta-analysis was conducted in WinBUGs version 1.4.3. The results are presented in **Table 277.**

Table 277: Baseline risk of surgical site bleeding, other major bleeding and clinically-relevant non-major bleeding on LMWH (standard dose, standard duration)

Outcome	THR % (SD)	TKR % (SD)
Surgical site bleeding	2.29% (0.025)	0.64% (0.016)
Other major bleeding	0.29% (0.005)	0.20% (0.021)
CRNMB	2.95% (0.013)	4.15% (0.038)

Abbreviations: CRNMB: clinically-relevant non-major bleeding; SD: standard deviation
(c) results of the unadjusted analysis
(d) defined as Cerebrovascular accident/gastrointestinal haemorrhage (non-fatal)

Baseline risk of HIT was based on the results of the systematic review and meta-analysis presented in the full guideline for the pairwise comparison of LMWH (std dose/extd duration) to LMWH (std dose/ std duration). Two trials were identified for the eTHR population,[208,534] and one for the eTKR population.[208] Based on these trials, the baseline risk of HIT is 0.17% (SE=0.00003) in eTHR and 0.92% (SE= 0.00062) in eTKR.

Mortality during the acute phase was modelled as the consequence of fatal PE, fatal MB and HIT. After the first 90 days and up to 12 years; mortality estimates were based on data from the 2016 NJR report which presented the mortality data by age band up to 12 years post the index operation. A polynomial function was fitted in Microsoft Excel to the reported cumulative mortality to calculate an annual probability of death.[109] Data from the NJR report are presented in Table 278.

Table 278: Mortality data for the first 12 years post primary operation by population

Time since primary operation (months)	Cumulative percentage mortality by population	
	THR	TKR

	Mean (a)	95% CI	Mean (a)	95% CI
1	0.22	0.21 to 0.23	0.17	0.16 to 0.18
3	0.48	0.47 to 0.50	0.32	0.31 to 0.33
12	1.49	1.46 to 1.52	1.05	1.03 to 1.07
36	4.90	4.85 to 4.96	4.13	4.08 to 4.18
60	9.51	9.43 to 9.59	8.64	8.56 to 8.71
84	15.05	14.95 to 15.16	14.45	14.35 to 14.56
120	24.88	24.70 to 25.06	25.68	25.50 to 25.87
144	28.51	28.28 to 28.74	34.11	33.76 to 34.46

Source: NJR report[109]
(a) Cumulative percentage probability of death weighted by age and sex.

Beyond 12 years post-primary THR or TKR; life tables for England for the years 2013 to 2015 were used as the source of the annual probability of death for males and females. Additionally, disease-specific mortality was modelled for those diagnosed with CTEPH.

P.1.3.4 Relative treatment effects

The between-strategy differences in costs and effects are driven by each strategy's relative risk (RR) reduction for VTE, and its RR increase for major bleeding. For example, the number of DVTs occurring under the rivaroxaban strategy is the baseline risk of DVT (when using the comparator LMWH (std dose/std duration)+ AEs) multiplied by the DVT RR reduction for rivaroxaban compared with LMWH (std dose/std duration) + AEs. The differential effects of treatment are only applied in the acute phase up to 90 days post-operatively (the decision tree part of the model) and treatment effect was not extrapolated beyond this time point. The sources of baseline risks and relative treatment effects are illustrated in **Table 279** and **Table 280**.

Table 279: Source of baseline risk and relative treatment effect for the primary and secondary outcomes in the decision tree part of the model- eTHR population

<table>
<tr><th>Outcome</th><th>All DVT</th><th>PE (non- fatal)</th><th>GI bleeding</th><th>ICH/ haemorrhagic stroke</th><th>SSB</th><th>Other MB</th><th>CRNMB</th></tr>
<tr><td>LMWH (std,std) + AEs</td><td>BR: Jameson 2011(b)</td><td>BR: Jameson 2011(b)</td><td colspan="2">BR: Jameson 2011 (b) & proportion of ICH from RCTs in the GL SR</td><td>BR: RCTs in the GL SR</td><td>BR: RCTs in the GL SR</td><td>BR: RCTs in the GL SR</td></tr>
<tr><td>LMWH (std,extd) + AEs</td><td rowspan="5">RR: DVT NMA</td><td rowspan="2">RR:PE NMA</td><td colspan="2" rowspan="5">RR: MB NMA</td><td rowspan="5">RR:MB NMA</td><td rowspan="5">RR: MB NMA</td><td>RR: ITC</td></tr>
<tr><td>Fondaparinux+ AES</td><td rowspan="4">RR: MB NMA</td></tr>
<tr><td>Foot pump + AES</td><td rowspan="2">RR:DVT NMA</td></tr>
<tr><td>IPCD</td><td rowspan="2">RR:PE NMA</td></tr>
<tr><td>AEs (above knee)</td></tr>
<tr><td>Foot pump</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

AES						
LMWH (std,std)						**RR:** ITC
LMWH (std,extd)						**RR:** ITC
Aspirin (std duration)			**RR:** Jameson 2011 (a)	**RR:** Jameson 2011(a)	**RR:** Jameson 2011(a)	**RR:** Jameson 2011(a)
LMWH (std, std) +Aspirin (extd duration)	**RR:** PE NMA		**RR:**MB NMA	**RR:** MB NMA	**RR:** MB NMA	**RR:** ITC
Dabigatran	**RR:** DVT NMA					**RR:** pairwise MA of RCTs in GL SR
Apixaban						**RR:** Pairwise MA
Rivaroxaban						Pairwise MA
No prophylaxis						**RR:** MB NMA

Abbreviations: AES: anti-embolism stockings; BR: baseline risk; CRNMB: clinically relevant non-major bleeding; DVT: deep vein thrombosis; eTHR: elective total hip replacement; GI: gastrointestinal; GL: guideline; ICH: intracranial haemorrhage; IPCD: intermittent pneumatic compressions device; ITC: indirect treatment comparison; LMWH :low molecular weight heparin; MA: meta-analysis; MB; major bleeding; NMA: network meta-analysis; RR: relative risk; SR: systematic review; SSB: surgical site bleeding; RCT: randomised controlled trials
Cells highlighted in dark grey indicate a different source of relative risk.to the outcome-specific NMA, ITC or pairwise MA.
(a) Source: Jameson 2011 [451]

Table 280: Source of baseline risk and relative treatment effect for the primary and secondary outcomes in the decision tree part of the model- eTKR population

Outcome	All DVT	PE (non-fatal)	GI bleeding	ICH/ haemorrhagic stroke	SSB	Other MB	CRNMB
LMWH (std,std) + AEs	**BR:** Jameson 2012 (b)	**BR:** Jameson 2012 (b)	**BR:** Jameson 2012 (b) & proportion of ICH from RCTs in the GL SR		**BR:** RCTs in the GL SR	**BR:** RCTs in the GL SR	**BR:** RCTs in the GL SR
Fondaparinux+ AES	**RR:** DVT NMA	**RR:** DVT NMA	**RR:** MB NMA		**RR:** MB NMA	**RR:** MB NMA	**RR:** MB NMA
Foot pump + AES		**RR:** DVT NMA					
IPCD		**RR:** PE NMA					
Foot pump		**RR:** DVT NMA					
AES		**RR:** PE NMA					
LMWH (std,std)							
LMWH (std,extd)							
Aspirin		**RR:** DVT	**RR:** Jameson 2012 (a)		**RR:**	**RR:**	**RR:**

		NMA		Jameson 2012 (a)	Jameson 2012 (a)	Jameson 2012 (a)
Dabigatran		**RR:** PE NMA	**RR:** MB NMA	**RR:** MB NMA	MB NMA	**RR:** pairwise MA of RCTs in GL SR
Apixaban						**RR:** pairwise MA of RCTs in GL SR
Rivaroxaban						**RR:** pairwise MA of RCTs in GL SR
No prophylaxis						**RR:** MB NMA

Abbreviations: AES: anti-embolism stockings; BR: baseline risk; CRNMB: clinically relevant non-major bleeding; DVT: deep vein thrombosis; eTKR: elective total knee replacement; GI: gastrointestinal; GL: guideline; ICH: intracranial haemorrhage; IPCD: intermittent pneumatic compressions device; LMWH :low molecular weight heparin; MA: meta-analysis; MB; major bleeding; NMA: network meta-analysis; RR: relative risk; SR: systematic review; SSB: surgical site bleeding; RCT: randomised controlled trials.
Cells highlighted in dark grey indicate a different source of relative risk.to the outcome-specific NMA, ITC or pairwise MA.
(a) Source: Jameson 2012[450]

P.1.3.4.1 DVT and PE

The RRs for each of the modelled strategies compared to LMWH (std/std) + AEs were obtained from the NMAs of the all DVT (symptomatic and asymptomatic) and non-fatal PE outcomes (see Appendix M for detail). These RRs have been calculated separately for each of the two populations. The absolute risks of each of these events for each prophylaxis strategy are presented in Table 281 and Table 282 below. These were calculated by multiplying the RRs obtained from the NMA by the baseline risk of each event on the model comparator.

Only where an intervention was in one of the NMAs but not in the other, it was agreed with the committee that the OR will be assumed the same as for the outcome for which data are available. This was based on an assumption of proportionality of effect on both VTE outcomes (DVT and PE). In the eTHR population, this was the case for only two interventions LMWH (std/std) followed by aspirin and foot pump+AES. For LMWH (std/std) followed by aspirin, no data were available for the outcome DVT (symptomatic and asymptomatic) and the OR obtained from the PE NMA was used instead. This assumption has also been tested in a sensitivity analysis (see section P.1.5), as the committee thought that the estimate obtained from the PE network was highly imprecise with very wide credible intervals. For the eTKR population, four interventions were not in the PE NMA and ORs from the DVT network were used instead. These were: fondaprinux+AES, foot pump, foot pump + AES and aspirin.

In the model, we apply the RR for all DVT to both symptomatic and asymptomatic DVT. Thus, if a certain strategy was shown to reduce DVTs by 60% then in the model the incidence of both symptomatic and asymptomatic DVT will be reduced by 60%.

Table 281: Absolute risk (95% CrI) of all DVT (symptomatic and asymptomatic) and non-fatal PE applied in the model for elective total hip replacement (eTHR)

Strategy	DVT (symptomatic and asymptomatic)	Non-fatal PE
1) LMWH (std,std) + AEs	5.54% (%5.39 to %5.70)	0.68% (%0.63 to %0.74)
2) LMWH (std,extd)+ AEs	4.03% (%0.53 to %14.34)	0.15% (%0.00 to %0.94)

Strategy	DVT (symptomatic and asymptomatic)	Non-fatal PE
3) Fondaparinux+ AES	3.25% (%0.46 to %11.43)	1.15% (%0.09 to %5.12)
4) Foot pump + AES	14.66% (%1.99 to %46.06)	1.48%(b)
5) IPCD	33.06% (%5.56 to %76.99)	5.28% (%0.15 to %31.35)
6) AEs (above knee)	8.30% (%0.87 to %48.85)	10.21% (%0.00 to %88.30)
7) Foot pump	28.01% (%2.41 to %78.81)	21.94% (%0.11 to %98.05)
8) AES	12.05% (%4.35 to %25.55)	1.18% (%0.08 to %5.46)
9) LMWH (std,std)	20.30% (%3.41 to %56.46)	2.47% (%0.18 to %12.53)
10) LMWH (std,extd)	9.76% (%0.97 to %36.66)	0.45% (%0.00 to %3.19)
11) Aspirin (std duration)	26.26% (%1.56 to %80.91)	36.63% (%0.35 to %99.62)
12) LMWH (std, std) + Aspirin (extd duration)	0.05%(a)	0.11% (%0.00 to %0.77)
13) Dabigatran	18.91% (%2.05 to %60.30)	3.56% (%0.13 to %20.41)
14) Apixaban	9.81% (%0.55 to %43.30)	2.01% (%0.05 to %12.24)
15) Rivaroxaban	4.00% (%0.27 to %18.33)	1.20% (%0.01 to %7.82)
16) No prophylaxis	40.42% (%9.59 to %81.09)	8.80% (%0.83 to %37.52)

Abbreviations: AES: anti-embolism stockings; CrI: credible interval; DVT: deep vein thrombosis; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compressions device; LMWH:low molecular weight heparin; PE: pulmonary embolism; std: standard

a) *Not in DVT NMA. Point estimate calculated based on the assumption that the relative effectiveness for the PE outcome compared to LMWH (std,std) + AES will be the same for the DVT.*

b) *Not in PE NMA. Point estimate calculated based on the assumption that the relative effectiveness for the DVT outcome compared to LMWH (std,std)+ AES will be the same for the PE.*

Table 282: Absolute risk (95% CrI) of DVT (symptomatic and asymptomatic) and non-fatal PE applied in the model for elective total knee replacement (eTKR)

Strategy	DVT (symptomatic and asymptomatic)	Non-fatal PE
1) LMWH (std,std) + AEs	14.00% (%13.81 to %14.20)	0.45% (%0.41 to %0.49)
2) Fondaparinux+ AES	12.51% (%3.76 to %27.50)	0.36% (a)
3) Foot pump + AES	18.96% (%9.45 to %33.25)	0.58%(a)
4) IPCD	21.23% (%7.04 to %42.74)	1.92% (%0.00 to %18.60)
5) Foot pump	8.38% (%1.12 to %26.89)	0.20% (a)
6) AES	29.97% (%15.13 to %48.19)	2.48% (%0.007 to %20.33)
7) LMWH (std,std)	9.22% (%2.98 to %20.08)	1.94% (%0.00 to %19.44)
8) LMWH (std,extd)	7.83% (%1.80 to %20.51)	0.87% (%0.000 to %6.25)

Strategy	DVT (symptomatic and asymptomatic)	Non-fatal PE
9) Aspirin	15.28% (%3.64 to %37.46)	0.43% (a)
10) Dabigatran	9.10% (%2.78 to %20.49)	5.06% (%0.00 to %60.15)
11) Apixaban	5.31% (%1.54 to %12.44)*	4.35% (%0.000 to %49.77)
12) Rivaroxaban	4.32% (%1.17 to %10.42)*	1.45% (%0.00 to %13.84)
13) No prophylaxis	34.21% (%13.98 to %58.93)	4.47% (%0.002 to %46.25)

Abbreviations: AES: anti-embolism stockings; CrI: credible interval; DVT: deep vein thrombosis; eTKR: elective total knee replacement; extd: extended; IPCD: intermittent pneumatic compressions device; LMWH: low molecular weight heparin; PE: pulmonary embolism; std: standard

a) *Not in PE network. Point estimate calculated based on the assumption that the relative effectiveness for the DVT outcome compared to LMWH (std,std)+ AES will be the same for the PE.*

P.1.3.4.2 Bleeding events

The main safety outcome included in the model is major bleeding. The odds ratios (ORs) for the included interventions compared to LMWH (std,std)+AEs were calculated from the NMA for non-fatal major bleeding. In the model, we use these ORs and the relevant baseline risk on LMWH (std,std)+AEs to calculate the absolute risk of each of the major bleeding events in the model (surgical site bleeding, stroke, GI bleeding , other major bleeding and fatal major bleeds). These ORs were also used to calculate the absolute risk of CRNMB when an intervention did not have trial data for this outcome. Wound haematoma and subsequent surgical site infection were modelled as consequences of CRNMB based on epidemiological data.

In the major bleeding NMA, we assumed that the major bleeding rate for mechanical only strategies is the same as for the no prophylaxis strategy and these were treated as one intervention (see Appendix M for the full NMA report). This was considered reasonable on biological grounds. The absolute risks of the bleeding events on each prophylaxis strategy are presented in Table 283 and Table 284 below.

Table 283: Absolute risk of the major bleeding and CRNMB events applied in the model for elective total hip replacement (eTHR)

Strategy	GI bleeding + ICH	SSB	Other major bleeding	CRNMB
1) LMWH (std,std) + AEs	0.72%	0.94%	0.30%	3.04%
2) LMWH (std,extd)+ AEs	0.77%	0.70%	0.23%	3.04%
3) Fondaparinux+ AES	1.40%	1.57%	0.51%	4.98%
4) Foot pump + AES	0.34%	0.36%	0.12%	1.18%
5) IPCD	0.34%	0.36%	0.12%	1.18%
6) AEs (above knee)	0.34%	0.36%	0.12%	1.18%
7) Foot pump	0.34%	0.36%	0.12%	1.18%
8) AES	0.34%	0.36%	0.12%	1.18%
9) LMWH (std,std)	0.72%	0.94%	0.30%	3.04%
10) LMWH (std,extd)	0.77%	0.70%	0.23%	3.04%
11) Aspirin (std duration)	0.79% (a)	1.03%	0.33%	3.29%
12) LMWH (std, std) + Aspirin (extd duration)	0.80%	0.10%	0.03%	1.64%

Strategy	GI bleeding + ICH	SSB	Other major bleeding	CRNMB
13) Dabigatran	1.19%	1.34%	0.43%	3.48%
14) Apixaban	1.17%	1.16%	0.37%	2.75%
15) Rivaroxaban	0.95%	0.99%	0.32%	3.68%
16) No prophylaxis	0.34%	0.36%	0.12%	1.18%

Abbreviations: AEs: anti-embolism stockings; DVT: deep vein thrombosis; extd: extended; LMWH: low molecular weight heparin; PE: pulmonary embolism; std: standard

(a) Source: Jameson 2011 [451]

Table 284: Absolute risk of the major bleeding and CRNMB events applied in the model for elective total knee replacement (eTKR)

Strategy	GI bleeding + ICH	SSB	Other major bleeding	CRNMB
17) LMWH (std,std) + AEs	0.39%	0.94%	0.21%	4.89%
18) Fondaparinux+ AES	4.20%	5.85%	1.34%	25.11%
19) Foot pump + AES	0.36%	0.88%	0.19%	4.58%
20) IPCD	0.36%	0.88%	0.19%	4.58%
21) Foot pump	0.36%	0.88%	0.19%	4.58%
22) AES	0.36%	0.88%	0.19%	4.58%
23) LMWH (std,std)	0.39%	0.94%	0.21%	4.89%
24) LMWH (std,extd)	0.43%	0.14%	0.03%	6.77%
25) Aspirin	0.38% (a)	0.93%	0.21%	4.84%
26) Dabigatran	0.44%	0.95%	0.21%	5.46%
27) Apixaban	0.34%	0.69%	0.15%	3.78%
28) Rivaroxaban	0.64%	1.33%	0.29%	5.83%
29) No prophylaxis	0.42%	0.88%	0.19%	4.58%

Abbreviations: AEs: anti-embolism stockings; DVT: deep vein thrombosis; extd: extended; LMWH: low molecular weight heparin; PE: pulmonary embolism; std: standard

(a) Source: Jameson 2012[450]

P.1.3.4.3 Complications of mechanical prophylaxis

Given the established evidence that some patients find stockings uncomfortable [985], this discomfort might cause patients to wear the stockings incorrectly (especially thigh-length stockings) – this might mean that the effectiveness estimated under trial conditions will not be replicated in practice. For this reason we included in the model the cost of nurse time for checking that mechanical prophylaxis options that require fitting and monitoring are fitted correctly. This will also ensure that complications can be avoided

P.1.3.5 Utilities

For economic evaluation, a specific measure of health-related quality of life (HRQoL) known as utility is required to calculate QALYs. Utilities indicate the preference for health states on a scale from 0 (death) to 1 (perfect health). The NICE reference case specifies that the preferred way for this to be assessed is by the EQ-5D instrument.

A systematic review of the literature was conducted to identify utility inputs to use in the model. Additionally, we examined the sources used in the economic evaluations retrieved in our main guideline economic search and existing NICE TAs.

P.1.3.5.1 Up to 90 days after surgery

For baseline utility values, we used EQ-5D-3L index values reported in the UK 2014-2015 PROMS programme.[683]The PROMS programme collects EQ-5D-3L data pre- and 6 months post-operatively for eTHR and eTKR patients.

The post-operative EQ-5D-3L index values reported in the PROMS data represents the utility at 6-12 months. We assumed that this value would be reached at the mean of the two time points (9 months). We also assumed a linear increase from the pre-operative utility score over the 6 months (180 days) to calculate the utility score at 90 days (the point of entry to the Markov model).

Bleeding events

We found three sources for the utility values for major bleeding events. We used the values reported by Locadia et al. 2004 for the major bleeding related outcomes (GI bleeding and stroke) as this study used time trade-off (TTO) for preference elicitation.[573] The relative utility decrements for the study population (mean age 55 years) were calculated and applied to the baseline utility in our model. These are listed in **Table 285.**

Table 285: Utility values for bleeding events and their sources

Event	Utility decrement	Source
Gastrointestinal bleeding	-32% (b)	Locadia 2004[573]
Haemorrhagic stroke-acute phase	-65%(b)	Locadia 2004[573]
CRNMB/Wound haematoma	-0.03 (c)	Sullivan 2011[927]

Abbreviations: CI: Confidence interval; CRNMB: clinically-relevant non-major bleeding.
(a) Calculated based on a SE of 10% around the mean
(b) time trade off (TTO). Relative utility decrement.
(c) EQ-5D. Absolute utility decrement

For those who develop other events during this period, an event-specific (Dis)utility was applied. The (dis)utilities and their sources are outlined in **Table 286.** The (dis)utilities for all events were applied as event-based after which the individual's quality of life would recover and continue on the post-operative linear improvement trajectory to achieve the utility value at 90-days post-operatively; except for surgical site infection that requires return to theatre or revision where it was assumed that the utility at 90 days post-operatively would be equal to that of post-infected revision/return to theatre for surgical site infection. This value was calculated based on data from Baker 2013, which reported on the QoI of individuals who had two-stage TKR revision for infection.[65]. The relative utility decrement and post-revision improvement reported in this study were assumed to be the same as for eTHR population (see **Table 286**). The timing of events, for the purpose of calculating QALYs, it was assumed that DVT and any adverse events (AEs) take place on day 7 while PE events take place on day 21. This was based on committee estimates. Data from Warwick 2007 were used in sensitivity analysis.[993]

Table 286: Base case (dis-)utility values for events up to 90 days

	Mean (dis-)utility	SE(a)	Source
No event (baseline utility at 90 days)	THR: 0.579 (BLU-THR)	0.057	PROMS 2014-2015[683]
	TKR: 0.582 (BLU-TKR)	0.058	PROMS 2014-2015[683]
Asymptomatic DVT- Distal	THR: 0.579 (BLU-THR)	0.057	PROMS 2014-2015[683]
Asymptomatic DVT- Proximal	TKR: 0.582 (BLU-TKR)	0.058	PROMS 2014-2015[683]
Symptomatic DVT- Proximal	-14%		Cohen 2014[192]
Symptomatic DVT- Distal	-14%		Assumption: equal to the disutility for symptomatic DVT-

	Mean (dis-)utility	SE(a)	Source
(requiring treatment)			proximal
Symptomatic DVT- Distal (not requiring treatment)	-7%		Assumption: equal to the 50% of the disutility for symptomatic DVT-proximal
Non-fatal PE	-19%		Cohen 2014[192]
Warfarin treated DVT or PE	-0.012		Marchetti 2001 [609] & Edoxaban TA354 [674]company submission
Major bleeding (surgical site, GI with or without intervention, other)	-32%		Locadia 2004[573]
ICH/acute stroke	-65%		Locadia 2004[573]
Pre- aseptic revision surgery	THR: 0.399	0.039	PROMS 2014-2015[683]
	TKR: 0.329	0.033	PROMS 2014-2015[683]
Post-aseptic revision surgery	THR: 0.538	0.054	PROMS 2014-2015[683]
	TKR: 0.459	0.046	PROMS 2014-2015[683]
Post-reoperation for surgical site MB	THR: 0.538	0.054	Assumed equal to post-aseptic revision
	TKR: 0.459	0.046	Assumed equal to post-aseptic revision
CRNMB (including wound haematoma)	-0.03		Sullivan 2011[927]
Surgical site infection	-66%		Baker 2013[65] for TKR, assumed the same for THR
Post-infected revision/return to theatre for surgical site infection	-30%		Baker 2013[65]for TKR, assumed the same for THR
HIT	-0.0712		Gould 1999 [355]
Post-HIT amputation	-0.28		Beaudet 2014, T1D GL[82]
Post-HIT thrombosis	-16.5%		Assumed average of PE and symptomatic proximal DVT dis-utilities
Post-HIT MB	-32%		Assumed equal to Major bleeding (surgical site, GI with or without intervention, other)
Fatal MB Fatal PE Death due to HIT	0.000		

Abbreviations: CRNMB: clinically-relevant non-major bleeding; GI: gastrointestinal; HIT: heparin-induced thrombocytopaenia; ICH: intracranial haemorrhage; MB: major bleeding; PE : pulmonary embolism; SE: standard error; THR: total hip replacement; TKR: total knee replacement.

(a) Where not reported; SE was calculated as 10% of the mean

P.1.3.5.2 > 90 days after surgery

For patients who have no event during the first part of the model, and progress to enter the "*well*" state in the Markov model, quality of life was adjusted for ageing as time passes in the model using age- and sex- specific disutility calculated from Kind 1998. [495]

The same utility value and aging disutility were used for individuals in the post-treated and post-untreated VTE health states ("*post- PE", "post-symptomatic proximal DVT", "post-symptomatic distal*

DVT", "post-asymptomatic proximal DVT", and "post-asymptomatic distal DVT"). For the remaining health states in the Markov model, the (dis)utilities and their sources are outlined in **Table 287**.

Table 287: Base case (dis-)utility values for the Markov model health states (more than 90 days after surgery)

	Mean (dis-)utility	SE(a)	Source	duration
Post stroke (disabled)	-10%		Lunde 2013 [586] 345 Stroke patients in Norway who had ischaemic/haemorrhagic or TIA	lifetime
Mild to Moderate PTS	-0.02		Lenert 1997 [548]	lifetime
Severe PTS	-0.07		Lenert 1997[548]	lifetime
CTEPH-Year 1	-26%		Meads 2008 [627]	Operable or inoperable (3 months) Recurrent/resistant (12 months)
CTEPH - Year 2- recurrent resistant Chronic CTEPH	22%		Meads 2008[627]	Utility improvement after medical treatment applied to CTEPH-Year 1 utility value Chronic CTEPH utility applied lifetime
Post-HIT amputation	-0.28		Beaudet 2014 [82], T1D GL[669]	Lifetime

Abbreviations: HIT: heparin-induced thrombocytopaenia; SE: standard error; T1D: Type 1 diabetes
a) Where not reported; SE was calculated as 10% of the mean

P.1.3.6 Resource use and costs

P.1.3.6.1 Prophylaxis strategies

The cost of the prophylaxis strategies included in the models was calculated based on the dose and duration of each of its components (pharmacological and/or mechanical). Additionally, the cost of administration and monitoring, where required, were included.

The total costs of each prophylaxis strategy are presented in

Table 288 for eTHR and eTKR populations. For a breakdown of the costs of the mechanical prophylaxis options, see **Table 289** and **Table 290** for the eTHR and eTKR populations; respectively. The unit costs of all pharmacological prophylaxis options are presented in **Table 291**. A breakdown of the costs of the pharmacological prophylaxis options including drug, administration and monitoring costs are also presented in **Table 292** and **Table 293** for the eTHR and eTKR populations; respectively. In calculating the costs of pharmacological prophylaxis options, oral administration was assumed to incur no costs. It was also assumed that there will be no drug wastage. A sensitivity anlysis has been undertaken taking wastage into account (see section P.1.5).

Table 288: Total costs of each prophylaxis strategy in the eTHR and eTKR models

Population and strategy	Total costs of pharmacological prophylaxis (I)	Total costs of mechanical prophylaxis (II)	Total intervention cost (I+II)
THR			
1. LMWH (std,std) + AEs	£138	£31	£169
2. LMWH (std,extd)+ AEs	£387	£31	£419
3. Fondaparinux+ AES	£83	£31	£115
4. Foot pump + AES	£0	£91	£91
5. IPCD	£0	£42	£42
6. AEs (above knee)	£0	£34	£34
7. Foot pump	£0	£59	£59
8. AES	£0	£31	£31
9. LMWH (std,std)	£138	£0	£138
10. LMWH (std,extd)	£387	£0	£387
11. Aspirin (std duration)	£0	£0	£0
12. LMWH (std, std) + Aspirin (extd duration)	£115	£0	£115
13. Dabigatran	£80	£0	£80
14. Apixaban	£59	£0	£59
15. Rivaroxaban	£74	£0	£74
16. No prophylaxis	£0	£0	£0
TKR			
1. LMWH (std,std) + AEs	£111	£31	£142
2. Fondaparinux+ AES	£97	£31	£128
3. Foot pump + AES	£0	£91	£91
4. IPCD	£0	£42	£42
5. Foot pump	£0	£59	£59
6. AES	£0	£31	£31
7. LMWH (std,std)	£111	£0	£111
8. LMWH (std,extd)	£355	£0	£355
9. Aspirin	£0	£0	£0
10. Dabigatran	£34	£0	£34
11. Apixaban	£23	£0	£23
12. Rivaroxaban	£25	£0	£25
13. No prophylaxis	£0	£0	£0

Abbreviations: AEs: anti-embolism stockings; eTKR: elective total knee replacement; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; std: standard

Table 289: Total costs of mechanical prophylaxis options - eTHR

Mechanical Prophylaxis	Price per pair (a) (I)	Prophylaxis duration (days) (b)	Number of Pairs (c) (II)	Total cost of consumables (Pairs)(d) (III)	Total Cost of fitting and monitoring (e) (IV)	Total Cost (f)
IPCD						
Knee length	£21.34	8.5	2	£43	£15	£58
Thigh length	£31.67	8.5	2	£63	£15	£78
Any length	£26.50(g)	8.5	2	£53	£15	£68
AES						
Knee length	£3.86	7	1	£4	£18	£22
Thigh length	£6.63	26	4	£27	£18	£45
Full length	£9.12	26	4	£37	£18	£55
Any length	£6.54 (g)	10.5	2	£13	£18	£31
Foot pump						
Foot Pump	£44.23 (h)	7	1	£44	£15	£60

Abbreviations: AEs: anti-embolism stockings; eTHR: elective total hip replacemen;t IPCD: intermittent pneumatic compression.

(a) Average price of sizes small to medium of IPC sleeves with vascular refill detection or stockings. Source: NHS supply chain catalogue 2015-2016[684]

(b) Average duration in the RCTs included in the NMA

(c) Calculated based on life expectancy of 7 days per pair and the duration of prophylaxis

(d) Calculated as (I) X (II).

(e) Cost of fitting was calculated based on average time required for fitting of IPCD/Foot pump and AEs of 5 minutes and 10 minutes, respectively. This was assumed to be completed by a band 5 hospital-based nurse (£35 per hour).[224] Cost of monitoring was assumed to require 5 minutes daily while in hospital. Similarly, this was assumed to be completed by a band 5 hospital-based nurse (£35 per hour).[224]

(f) Calculated for the duration of prophylaxis as the sum of (III) and (IV).

(g) Calculated as average of all lengths.

(h) Source: Price used in CG92 model was adjusted for inflation using the PSSRU hospital & community health services (HCHS) index.[224]

Table 290: Total costs of mechanical prophylaxis options - eTKR

Mechanical Prophylaxis	Price per pair (a) (I)	Prophylaxis duration (days) (b)	Number of Pairs (c) (II)	Total cost of consumables (Pairs)(d) (III)	Total Cost of fitting and monitoring (e) (IV)	Total Cost (f)
IPCD						
Knee length	£21.34	6	1	£21	£15	£37
Thigh length	£31.67	6	1	£32	£15	£47
Any length	£26.50 (g)	6	1	£27	£15	£42
AEs						
Knee length	£3.86	10.5	2	£8	£18	£26
Thigh length	£6.63	10.5	2	£13	£18	£31
Full length	£9.12	10.5	2	£18	£18	£36
Any length	£6.54 (g)	10.5	2	£13	£18	£31
Foot pump						
Foot Pump	£44.23 (h)	4	1	£44	£15	£59

Abbreviations: AEs: anti-embolism stockings; eTKR: elective total knee replacement; IPCD: intermittent pneumatic compression.

(a) Average price of sizes small to medium of IPC sleeves with vascular refill detection or stockings. Source: NHS supply chain catalogue 2015-2016.[684]
(b) Average duration in the RCTs included in the NMA
(c) Calculated based on life expectancy of 7 days per pair and the duration of prophylaxis
(d) Calculated as (I) X (II).
(e) Cost of fitting was calculated based on average time required for fitting of IPCD/Foot pump and AEs of 5 minutes and 10 minutes, respectively. This was assumed to be completed by a band 5 hospital-based nurse (£35 per hour).[224] Cost of monitoring was assumed to require 5 minutes daily while in hospital. Similarly, this was assumed to be completed by a band 5 hospital-based nurse (£35 per hour).).[224]
(f) Calculated for the duration of prophylaxis as the sum of (III) and (IV).
(g) Calculated as average of all lengths.
(h) Source: Price used in CG92 model was adjusted for inflation using the PSSRU hospital & community health services (HCHS) index.[224]

Table 291: Unit costs of pharmacological prophylaxis

Drug	Preparation	strength	Mg or IU/ unit	Units / pack	Cost/ pack (£)	Cost/ unit (£)	Units / day	Cost/ day (£)	Cost/ month (£)
Enoxaparin sodium	solution for injection pre-filled syringes	40mg/ 0.4ml	40	10	£30.27 (a)	£3.03	1	£3.0	£92
Dalteparin sodium	Solution for injection- pre-filled syringes	5,000 units/ 0.2ml	5,000	10	£28.23 (b)	£2.82	1	£2.8	£86
Tinzaparin sodium	Solution for injection- pre-filled syringes	3500units /0.35ml	3,500	10	£27.71 (b)	£2.77	1	£2.8	£84
Tinzaparin sodium	Solution for injection- pre-filled syringes	4500units /0.45ml	4,500	10	£35.63 (b)	£3.56	1	£3.6	£108
Fondaparinux sodium	solution for injection pre-filled syringes	2.5 mg/ 0.5ml	2.5	10	£43.95 (c)	£4.40	1	£4.4	£134
Dabigatran etexilate	capsules	110 mg	110	60	£65.90 (a)	£1.10	1	£1.1	£33
Dabigatran etexilate	capsules	110 mg	110	60	£65.90 (a)	£1.10	2	£2.2	£67
Dabigatran etexilate	capsules	150 mg	150	60	£65.90 (a)	£1.10	1	£1.1	£33
Dabigatran etexilate	capsules	75 mg	75	60	£65.90 (a)	£1.10	1	£1.1	£33
Rivaroxaban	tablets	10 mg	10	30	£63.00 (a)	£2.10	1	£2.1	£64
Apixaban	tablets	2.5 mg	2.5	60	£57.00 (a)	£0.95	2	£1.9	£58
Aspirin	tablets	300 mg	300	32	£3.35 (a)	£0.10	1	£0.1	£3

(a) NHS Drug tariff July 2016[682]
(b) British National Formulary[458]
(c) eMIT/CMU[207]

Table 292: Total costs of pharmacological prophylaxis for the eTHR population

Drug	Dose	RCT duration (a)	Licensed duration (b)	Initiation	Cost category	Total costs
LMWH (standard duration)	**(c)**	**16**	**N/A**	**Post-op**	Drug cost	£41.14
					Administration costs	£91.30
					Monitoring tests	£47.47
					Total cost	**£179.91**
LMWH (standard duration)	**(c)**	**11**	**N/A**	**Pre-op**	Drug cost	£25.85
					Administration costs	£37.40
					Monitoring tests	£32.37
					Total cost	**£95.61**
LMWH (extended duration)	**(c)**	**33**		**Pre-op**	Drug cost	£92.81
					Administration costs	£242.73
					Monitoring tests	£51.79
					Total cost	**£387.33**
Fondaparinux sodium (standard duration)	**2.5 mg once daily (dose is weight based)**	**8**	**N/A**	**post-op**	Drug cost	£30.77
					Administration costs	£26.77
					Monitoring tests	£25.89
					Total cost	**£83.42**
Dabigatran etexilate	**Dose is age-based (75 to 110 mg once to twice daily)**	**32**	**27-34**	**post-op**	Drug cost	£67.00
					Administration costs	£0.00
					Monitoring tests	£12.95
					Total cost	**£79.94**
Rivaroxaban	**10 mg once daily**	**35**	**35**	**post-op**	Drug cost	£73.50
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£73.50**
Apixaban	**2.5 mg once**	**32**	**32-38**	**post-op**	Drug cost	£58.90

Drug	Dose	RCT duration (a)	Licensed duration (b)	Initiation	Cost category	Total costs
	daily					
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£58.90**
Aspirin	**100 mg daily (d)**	**7**	**N/A**	**post-op**	Drug cost	£0.24
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£0.24**
LMWH (10 days)+ Aspirin (28 days)	**LMWH: (c) Aspirin: 100 mg daily (d)**	**38**	**N/A**	**Postop**	Drug cost	£29.71
					Administration costs	£53.17
					Monitoring tests	£32.37
					Total cost	**£115.25**

(a) average duration in the relevant randomised controlled trials included in the NMAs. For LMWH, this is the average for across all the trials of all included drugs (enoxaparin, tinzaparin and daltparin)
(b) Source: British National Formulary British National Formulary[458]
(c) Enoxaparin: 40 mg once daily, tinzaparin: 3500 units/day, dalteparin:5000IU/day
(d) Dose as used in the included trials

Table 293: Total costs of pharmacological prophylaxis for the eTKR population

Drug	Dose	RCT duration (a)	Licensed duration (b)	Initiation	Cost category	Total costs
LMWH (standard duration)	**(c)**	10	N/A	Post-op	Drug cost	£28.74
					Administration costs	£53.17
					Monitoring tests	£32.37
					Total cost	**£114.27**
LMWH (standard duration)	**(c)**	10	N/A	Pre-op	Drug cost	£28.74
					Administration costs	£46.20
					Monitoring tests	£32.37
					Total cost	**£107.30**
LMWH (extended duration)	**(c)**	30	N/A	Post-op	Drug cost	£83.34
					Administration costs	£220.37
					Monitoring tests	£51.79

Drug	Dose	RCT duration (a)	Licensed duration (b)	Initiation	Cost category	Total costs
					Total cost	**£355.49**
Fondaparinux sodium	**2.5 mg once daily (dose is weight based)**	11	N/A	Post-op	Drug cost	£43.95
					Administration costs	£53.17
					Monitoring tests	£0.00
					Total cost	**£97.12**
Dabigatran etexilate	**Dose is age-based (75 to 110 mg once to twice daily)**	11	9	Post-op	Drug cost	£20.87
					Administration costs	£0.00
					Monitoring tests	£12.95
					Total cost	**£33.81**
Rivaroxaban	**10 mg once daily**	13	14	Post-op	Drug cost	£25.20
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£25.20**
Apixaban	**2.5 mg once daily**	12	10 to 14	Post-op	Drug cost	£22.80
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£22.80**
Aspirin	**100 mg daily (d)**	14	N/A	Post-op	Drug cost	£0.49
					Administration costs	£0.00
					Monitoring tests	£0.00
						£0.49

(a) average duration in the relevant randomised controlled trials included in the NMAs. Fir LMWH, this is the average for across all the trials of all included drugs (enoxaparin, tinzaparin and daltparin)
(b) Source: British National Formulary British National Formulary[458]
(c) Enoxaparin: 40 mg once daily, tinzaparin: 3500 units/day, dalteparin:5000IU/day
(d) Dose as used in the included trials

P.1.3.6.2 Decision tree events (up to 90 days post-operatively)

P.1.3.6.2.1 Pulmonary Embolism (PE) and symptomatic DVT treatment

Micro-costing was undertaken to calculate the cost of treating non-fatal PE and symptomatic proximal DVT episodes, as the guideline committee felt that the NHS reference costs did not reflect recent advances in current practice where both DVT and PE are generally treated on outpatient basis

and if a hospital admission is required for PE, this would be either a short stay or day case admission. Additionally, the guideline committee wanted to reflect the fact that PE events occurring in hospital pre-discharge would only require, on average, one excess bed day and unlikely to result in a delay in discharging patients.

The total cost of diagnosis and treatment for these VTE events was, thus, calculated to include the following cost categories: diagnosis, drug treatment and other resources. Unit costs were taken from standard NHS sources: NHS Electronic Drug Tariff,[682] NHS Schedule for Reference Costs 2015-2016[250], British National Formulary (June 2016)[458], eMIT/CMU,[207] and Unit Costs of Health and Social Care 2016.[224]

Diagnosis:

The pathways for objective confirmation of the diagnosis of symptomatic DVT and PE were based on NICE guideline CG144.[668] costs of diagnosing symptomatic DVT and PE are presented in **Table 294** and **Table 295**; respectively. A weighted average cost for events occurring in-hospital (pre-discharge) and those occurring in community (post-discharge) was calculated for each event on the assumption that 25% of events occur post-discharge.

For DVT; the weighted average cost was calculated to be £62 for proximal and £92 for distal DVT. For PE; events occurring post-discharge were assumed to require an inpatient admission and hence, diagnosis costs if occurring post-discharge were assumed to be £0 as diagnostic investigations would be included in the cost of the admission episode.

Table 294: Diagnosis costs for symptomatic DVT

	Units used	Breakdown of Resources used per unit	Unit cost	Source for unit cost	Total cost	% of patients		Weighted average cost
						In hospital	Post-discharge	
Wells Score	1	10 minutes of registrar time.	£10.06 [£60.33 per hour (weighted average cost of all working hours, including qualification)]	PSSRU 2016[224]	£10.06	100%	0% (assumed to be completed as part of a GP or ED visit)	
DDi-laboratory based	1	One DDi test	£20.79 [£207.88 per pack of 10]	Supply chain catalogue 2015-2016[684]	£31.65	7% (proximal DVT)[353] 100% (distal DVT)	7% (proximal DVT)[353] 100% (distal DVT)	
		5 minutes of a laboratory technician time	£2.00 [£24 per hour (allied health professional)]	PSSRU 2016				
		10 minutes of a hospital-based clinical support worker (nursing)-band 2	£3.83 [£23 per hour of patient contact(including qualification)]	PSSRU 2016[224]				
		5 minutes of a registrar time	£5.03 [£60.33 per hour (weighted average cost of all working hours, including qualification)]	PSSRU 2016[224]				

	Units used	Breakdown of Resources	Unit cost	Source for unit cost	Total cost	% of patients		Weighted average
Proximal Leg Vein Ultrasound (PLV-US)-direct access	1	Leg ultrasound for less than 20 minutes for each leg.	Direct access: £55.12 per test Outpatient: £52.20 per test [weighted average of Leg ultrasound for less than 20 minutes for each leg with and without contrast (currency codes RD41Z and RD40Z respectively)]	National Schedule of Reference Costs - Year 2015-2016[250]	£55.12 £52.20	100%	50% 50%	
						In-hospital	**Post-discharge**	**Weighted average (a)**
					Proximal DVT	£64.47	£55.87	£62.32
					Distal DVT	£93.90	£85.31	£91.75

Abbreviations: DDi: D-Dimer, DVT: deep vein thrombosis.

a) *Calculated based on a proportion of DVTs happening in hospital of 75% while 25% would be diagnosed post discharge.*

Table 295: Costs of diagnosing PE events occurring in-hospital (pre-discharge)

	Units used	Breakdown of Resources used per unit	Unit cost	Source for unit cost	Total cost	% of patients In-hospital
Chest X-ray	1	Direct Access Plain Film	£30.26[HRG code DAPF]	National Schedule of Reference Costs - Year 2015-2016 [250]	£30.26	100%
Two level PE Wells Score	1	10 minutes of registrar time.	£10.06 [£60.33 per hour (weighted average cost of all working hours, including qualification)]	PSSRU 2016[224]	£10.06	100%
DDi-laboratory based	1	One DDi test	£20.79 [£207.88 per pack of 10]	Supply chain catalogue 2015-2016[684]	£31.65	75%
		5 minutes of a laboratory technician time	£2.00 [£24 per hour (allied health professional)]	PSSRU 2016[224]		
		10 minutes of a hospital-based clinical support worker (nursing)-band 2	£3.83 [£23 per hour of patient contact(including qualification)]	PSSRU 2016[224]		
		5 minutes of a registrar time	£5.03 [£60.33 per hour (weighted average cost of all working hours, including qualification)]	PSSRU 2016[224]		
CTPA	1	Computerised Tomography Scan of one area, with post contrast only,	£102.01 [weighted average cost of HRG codes RD21A(19 years and over) and RD21B (between 6 and 18 years)	National Schedule of Reference Costs - Year 2015-2016[250]	£102.01	90%
V/Q Spect	1	Single Photon Emission Computed Tomography (SPECT)	£263.56 [weighted average cost of HRG codes RN08A (19 years and over) and RN08B (between 6 and 18 years)	National Schedule of Reference Costs - Year 2015-2016[250]	£263.56	5%
V/Q planar	1	Lung Ventilation or Perfusion Scan, 19 years	£245.77 [weighted average cost of HRG codes RN18A (19 years and over)	National Schedule of Reference Costs - Year	£245.77	5%

	Units used	Breakdown of Resources used per unit	Unit cost	Source for unit cost	Total cost	% of patients In-hospital
		and over	and RN18B (between 6 and 18 years)	2015-2016[250]		
					Total	£181.33

Drug treatment:
Strategies for the treatment of DVT and PE were based on CG144, the recent edoxaban technology appraisal for VTE treatment and secondary prevention (TA354) and the guideline committee expert opinion. [674] The guideline committee advised that the duration of the treatment course for symptomatic DVT and PE would be 3 months, given that hospital acquired VTE is a provoked event. Three strategies for treatment were considered to be the standard recommended treatment pathways.

The first strategy (Strategy 1) is the traditional approach to treatment where a parenteral anticoagulant is given from diagnosis for up to day 7; overlapping with an oral Vit. K antagonist (warfarin). The parenteral anticoagulants considered were LMWHs (enoxaparin, dalteparin or tinzaparin), UFH or fondaparinux. The Vit K antagonist is then continued up to 3 months. The second strategy (Strategy 2) involves using the direct acting oral anticoagulants (DOACs) rivaroxaban or apixaban from day 0 up to 3 months. The third strategy (Strategy 3) involves the use of a parenteral anticoagulant for 7days followed by one of the two DOACs: dabigatran or edoxaban for the remainder of the 3 months treatment duration.

The cost of each strategy was calculated using the following doses:

- LMWHs (for 7 days):
    - Dalteparin : 15,000-unit (0.6-mL) syringe.
    - Tinzaparin : 14,000-unit (0.7-mL) syringe.
    - Enoxaparin : 100-mg (1-mL, 10 000-units) syringe.
- UFH: 5,000 units/mL:5-mL amp.
- Fondaparinux: body-weight under 50 kg, 5 mg every 24 hours; body-weight 50–100 kg, 7.5 mg every 24 hours; body-weight over 100 kg, 10 mg every 24 hours
- Warfarin: on average 5 mg twice daily
- Rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily)
- Apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily)
- Dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age) following acute phase parenteral anticoagulation
- Edoxaban (60 mg once daily) following acute-phase parenteral anticoagulation

The unit costs for these drug regimens are presented in **Table 296.**

The costs of administration, monitoring and follow-up, where applicable, were also included (see **Table 297**). The cost of anticoagulation clinics was also included in strategy 1 where a Vit K antagonist is used. Self-administration of parenteral treatments was considered to occur in a similar proportion of patients to that used for calculating the cost of the parenteral prophylaxis interventions (80%). The cost of nurse education for self-administration and the costs of sharps bins were included for these patients. For patients requiring nurse administration, the cost of nurse time was included.

The committee advised that the first two of these are the most commonly used in practice; hence; a weighted average cost of treatment was calculated as the weighted average of these two strategies in a ratio of 1:1 in the base case analysis. The total cost of each strategy is presented in **Table 298**.

Table 296: Drug costs for VTE treatment regimens

Drug	Preparation	Mg or IU/ unit	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Cost/ mg or IU (£)	Units/ day	Cost/ day (£)	Cost/ month (£)
Parentral anticoagulants									
LMWHs									
Enoxaparin sodium	solution for injection pre-filled syringes	100	10	£72.3 (a)	£7.23	£0.07	1	£7.23	£219.91
Dalteparin sodium	Solution for injection- pre-filled syringes	15,000	5	£42.34 (b)	£8.47	£0.001	1	£8.47	£257.57
Tinzaparin sodium	solution for injection- pre-filled syringes	14,000	6	£49.98 (b)	£8.33	£0.001	1	£8.33	£253.37
Unfractionated heparin (UFH)									
Heparin sodium	solution for injection- ampoules	5,000	10	£13.89 (c)	£1.39	£0.0003	1	£1.39	£42.25
Pentasaccharide									
Fondaparinux sodium	solution for injection pre-filled syringes	5	10	£84.22 (c)	£8.42	£1.68	1	£8.42	£256.17
Fondaparinux sodium	solution for injection pre-filled syringes	7.5	10	£86.92 (c)	£8.69	£1.16	1	£8.69	£264.38
Fondaparinux sodium	solution for injection pre-filled syringes	10	10	£89.38 (c)	£8.94	£0.89	1	£8.94	£271.86
Vit K antagonists									
Warfarin sodium	tablets	5	28	£0.82(a)	£0.03	£0.01	2	£0.06	£1.78
Direct-acting Oral Anticoagulants (DOACs)									
Rivaroxaban	tablets	15	28	£58.80(a)	£2.10	£0.14	2	£4.20	£127.75
Rivaroxaban	tablets	20	28	£58.80(a)	£2.10	£0.11	1	£2.10	£63.88
Apixaban	tablets	5	28	£26.60 (b)	£0.95	£0.19	4	£3.80	£115.58
Apixaban	tablets	5	56	£53.20 (b)	£0.95	£0.19	2	£1.90	£57.79

Drug	Preparation	Mg or IU/ unit	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Cost/ mg or IU (£)	Units/ day	Cost/ day (£)	Cost/ month (£)
Dabigatran etexilate	capsules	150	60	£65.90 (a)	£1.10	£0.01	2	£2.20	£66.82
Edoxaban (as tosilate)	tablets	60	28	£51.80 (b)	£1.85	£0.03	1	£1.85	£56.27

Abbreviations: DOACs: directly-acting oral anticoagulants; IU: international unit; LMWH: low molecular weight heparin; UFH: unfractionated heparin;
(a) NHS Electronic Drug Tariff[682]
(b) British National Formulary (June 2016)[458]
(c) eMIT/CMU[207]

Table 297: Administration and monitoring costs for drugs used for VTE treatment

Treatment	Tests required	total Cost of tests per 3 months treatment	Nurse time associated with administering and monitoring prophylaxis	Cost of Nurse education of self-injection	Cost of nurse time per day of hospital stay	Cost of nurse time per day in community	Cost of Sharps bin	Other costs	Total cost of monitoring and administration	
									Sympt DVT	PE
LMWH	Full blood count: baseline then every 2-4 days until day 14 (BCSH guidelines, Keeling 2006 [481])	£29.13	2-3 minutes per injection	£4.40	£1.83	£8.80	£2.21	-	£97.34	£90.37
UFH	Full blood count: baseline (plus the day after start if previous exposure to UFH) then alternate days from day 4-14 (BCSH guidelines, Keeling 2006[481])	£29.13	2-3 minutes per injection	£4.40	£5.50	£26.40	£2.21	-	£220.54	£199.64
Warfarin	prothrombin time (PT) once at the start, International Normalised	£97.10	10-20 minutes per day	-	£11.00	-	-	£116.91 (a)	£97.10	£108.10

Treatment	Tests required	total Cost of tests per 3 months treatment	Nurse time associated with administering and monitoring prophylaxis	Cost of Nurse education of self-injection	Cost of nurse time per day of hospital stay	Cost of nurse time per day in community	Cost of Sharps bin	Other costs	Total cost of monitoring and administration	
									Sympt DVT	PE
	Ratio (INR) tests: approximately 3 per week during hospital stay then less frequently at least once every 12 weeks									
Fondaparinux	-	-	2-3 minutes per injection	£4.40	£1.83	£8.80	£2.21	-	£68.21	£12.95
Apixaban	-	-	-	-	-	-	-	-	-	-
Dabigatran	Baseline liver and renal function test	£12.95	-	-	-	-	-	-	£12.95	£12.95
Edoxaban	Baseline liver and renal function test	£12.95	-	-	-	-	-	-	£12.95	£12.95
Rivaroxaban	-	-	-	-	-	-	-	-	-	-

Abbreviations: DVT: deep vein thrombosis; LMWH: low molecular weight heparin; PE: pulmonary embolism; UFH: unfractionated heparin;
(a) Anticoagulation clinic costs (1 first visit and 3 monthly follow-up visits)

Table 298: Total costs for each VTE treatment strategy

Drug class	Drug	% of patients	Days on treatment	Drug cost per treatment course - PE/DVT	Monitoring and administration for period of treatment- PE	Monitoring and administration for period of treatment- DVT	Total costs	
							PE	DVT
Strategy 1							**£372.18**	**£368.85**
Parentral Anticoagulant		100%						

Drug class	Drug			% of patients	Days on treatment	Drug cost per treatment	Monitoring and administration for period of	Monitoring and administration for period of	Total costs	
LMWH	enoxaparin	dalteparin	tinzaparin							
	45% (a)	27% (a)	18% (a)	90%(b)	7	£49.27(b)	£90.37	£97.34	£139.65	£149.65
UFH				5% (b)	7	£9.72	£199.64	£220.54	£209.36	£230.26
Fondaparinux				5% (b)	7	£60.84	£61.24	£68.21	£122.09	£129.05
Vit K antagonist	Warfarin			100%	84	£4.92	£225.01	£214.01	£229.93	218.93
Strategy 2									**£196.70**	**£196.70**
Direct-acting oral anticoagulants (DOACs)	Apixaban			50%	84	£172.90	£0.00	£0.00	£172.90	£172.90
	Rivaroxaban			50%	84	£220.50	£0.00	£0.00	£220.50	£220.50
Strategy 3									**£311.00**	**£318.66**
Parentral Anticoagulant				100%						
LMWH	enoxaparin	dalteparin	tinzaparin							
	45% (a)	27% (a)	18% (a)	90%(b)	7	£49.27(b)	£90.37	£97.34	£139.65	£149.65
UFH				5% (b)	7	£9.72	£199.64	£220.54	£209.36	£230.26
Fondaparinux				5% (b)	7	£60.84	£61.24	£68.21	£122.09	£129.05
Direct-acting oral anticoagulants (DOACs)	Dabigatran			50%	77	£169.14	£12.95	£12.95	£182.09	£182.09
	Edoxaban			50%	77	£142.45	£12.95	£12.95	£155.40	£155.40

Abbreviations: DOACs: directly-acting oral anticoagulants; DVT: deep vein thrombosis; LMWH: low molecular weight heparin; PE: pulmonary embolism; UFH: unfractionated heparin; VTE: venous thromboembolism

(a) Proportions expert opinion as reported in TA354 [674]

(b) Proportions expert opinion as reported in TA354 [674]

(c) Average cost of the three LMWHs weighted by the probability of prescribing each of them.

Other resources:

For symptomatic DVT events diagnosed pre-discharge, no extra resources were included. In case of PE, an excess bed day was included for all patients as well as a critical care admission for 10% of patients. For events occurring post discharge, it was assumed that a visit to either the GP or the emergency department will be required during which initial assessment will be undertaken. The cost of an ambulance transfer was included for patients who will require an emergency department visit. The cost of short stay admission was also included for all patients diagnosed with PE and 50% of patients diagnosed with a symptomatic proximal DVT (see **Table 299** and **Table 300**).

Table 299: Resource use for PE events

	% of Patients		
Resource item	**In-hospital**	**Post-discharge**	**unit cost**
Emergency department visit	0%	80%	£222(a)
GP visit	0%	20%	£36 (b)
PE admission short stay	0%	100%	£499 (c)
Critical care unit stay	10%	10%	£1,021(d)
Ambulance	0%	80%	£236 (e)
Excess bed days-Hip	100%	0%	£333 (f)
Excess bed days-knee	100%	0%	£335 (g)
Total	**In-hospital**	**Post-discharge**	**Weighted average cost**
eTHR	£435.10	£975.46	**£570.19**
eTKR	£437.01	£975.46	**£571.63**

Abbreviations: eTHR: elective total hip replacement; eTKR: elective total knee replacement;.GP: general practitioner; PE: pulmonary embolism.

(a) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of Type 01 and Type02 admitted emergency department HRG codes VB01Z to VB09Z.

(b) PSSRU 2016[224]

(c) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of non-elective short stay for "Pulmonary Embolus with Interventions", codes DZ09J to DZ09N, DZ09P and DZ09Q.

(d) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of adult Critical Care, 0 to 6 or more organs Supported, codes XC01Z to XC01Z.

(e) NHS Schedule for Reference Costs 2015-2016[250]. "See and treat and convey", code ASS02.

(f) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of elective inpatient excess bed days for "Very Major Hip Procedures for Non-Trauma" CC score 0 to 10+, codes HN12A to HN12F.

(g) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of elective inpatient excess bed days for "Very Major knee Procedures for Non-Trauma" CC score 0 to 8+, codes HN22A to HN22E.

Table 300: Resource use for symptomatic DVT events

	% of Patients		
Resource item	**In-hospital**	**Post-discharge**	**unit cost**
Emergency department visit	0%	50%	£222(a)
GP visit	0%	50%	£36 (b)
DVT admission short stay	0%	50% (proximal) 0% (distal)	£403 (d)
Ambulance	0%	50%	£236 (e)
Total	**In-hospital**	**Post-discharge**	**Weighted average cost**
Symptomatic proximal	£0.00	£448.85	**£112.21**
Symptomatic distal	£0.00	£247.21	**£61.80**

Abbreviations: DVT: deep vein thrombosis; eTHR: elective total hip replacement; eTKR: elective total knee replacement; GP: general practitioner.

(a) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of Type 01 and Type02 admitted emergency department HRG codes VB01Z to VB09Z.
(b) PSSRU 2016[224]
(c) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of non-elective short stay for "Deep Vein Thrombosis" CC score 0 to 12+, codes YQ51A to YQ51E.
(d) NHS Schedule for Reference Costs 2015-2016[250]. "See and treat and convey", code ASS02.

In clinical practice there would be no diagnosis or treatment costs associated with asymptomatic DVT (proximal and distal). Hence, the costs of these events were assumed to be £0. Similarly, in line with CG92 model assumptions; the incremental treatment cost of fatal pulmonary embolism (and fatal bleeding) was assumed to be £0 - on the one hand treatment of the event would generate additional health service costs but on the other hand the treatment costs for the illness they were admitted will be curtailed.

P.1.3.6.2.2 Major bleeding

The cost of managing major bleeding was calculated based on the site of bleeding and the need to re-operate. Antidote costs were not explicitly incorporated.

For **gastro-intestinal bleeding**, it was assumed that an intervention would be required in 13% of cases, based on a review of five fondaparinux and dabigatran trials.[666] The cost for managing a GI bleed that requires an intervention was based on the NHS schedule for Reference costs 2015-2016 HRG codes FZ38J to FZ38L (Gastrointestinal Bleed with Single Intervention, with CC Score 0-4 to 8+) for non-elective short stay, non-elective long stay and elective long stay. This was £2,409. The cost for managing a GI bleed that does not require an intervention was based on the NHS schedule for Reference costs 2015-2016 HRG codes FZ38M to FZ38P (Gastrointestinal Bleed without Interventions, with CC Score 0-4 to 9+) for non-elective short stay, non-elective long stay and elective long stay98890. This was £855.[250]

For **surgical site bleeding**, it was assumed that it will lead to a return to theatre in 100% of cases based on the definition in the trials that reported it. The cost was considered to be equal to that of the primary operation: £6,278 for eTHR and £6,178 for eTKR. For eTHR, the cost was the weighted average of HRG codes HN12A to HN12F (Very Major Hip Procedures for Non-Trauma with CC Score from 0-1 to 10+) and for eTKR, the cost was the weighted average of HRG codes HN22A to HN22E (Very Major Knee Procedures for Non-Trauma with CC Score from 0-1 to 8+).

For **intracranial haemorrhage/haemorrhagic stroke**, the cost of the acute event management was calculated as the weighted average cost for the HRG codes AA35A to AA35F (Stroke with CC Score 0-3 to 16+), non-elective long stay, to be £4,354. Other costs during the first 90 days were calculated as the average of managing a patient with stroke in the first year for a dependent state and for an independent state for 90 days out of the full year. This was £3,255. Hence, the total cost for managing the stroke event in the first 90 days was calculated to be £7,609.

For **bleeding at any other site**, the cost was assumed to be the same as for GI bleeding that does not require an intervention (£855).[250]

P.1.3.6.2.3 Clinically-relevant non-major bleeding

The cost of managing a CRNMB that is diagnosed post-discharge was assumed to be the cost of two outpatient visits-trauma and orthopaedics. The first visit cost was calculated to be £133, which is a weighted average cost of consultant-led and non-consultant-led, for a non-admitted face to face attendance, first visit. The follow-up visit cost was calculated to be £108.3, which is a weighted average cost of consultant-led and non-consultant-led, for a non-admitted face to face attendance, follow-up visit. Hence, the total cost of managing a CRNMB event was £241.6. For events that occur in-hospital; no extra cost was factored in and hence; the cost was assumed to be £0.

For CRNMB events that lead to a **surgical-site infection**, however, the cost of medically managing the surgical site infection was calculated to be £3,696. This was the weighted average cost of HRG codes HD25D (Infections of Bones or Joints, with CC Score 0-1 to 13+) for non-elective short, non-elective long and elective inpatient stays. For surgical site infections that will require surgical intervention, the cost was assumed to be a weighted average of the cost of a return to theatre and that of a revision for infection.

The cost of a **return to theatre** was assumed to be the same as a primary operation (£6,278 for eTHR and £6,178 for eTKR). The cost of a **revision for infection** was calculated based on published UK data which reported that the cost of a two-stage revision for TKR was £30,011 (cost year 2013). In the same study, the cost of a primary TKR was reported to be £9,655 which was higher than the cost or a primary eTKR in our model. Hence, it was decided that rather than using the cost of a revision directly from the study and adjusting for inflation that a ratio of the cost of the revision for infection to that of the primary operation in the same study be used instead. This ratio was calculated to be 3.11 (£30,011/£9,655). This ratio was, thus, applied to the cost of primary eTKR in the model (£6,178) to calculate the cost of the revision for infection (£19,203). Based on the committee's expert opinion, it was considered appropriate to apply this ratio also to the eTHR primary operation cost to calculate the cost of the revision for infection for eTHR. Hence, the cost of a revision for infection for eTHR was calculated as £6,278*3.11 to be £19,514.

P.1.3.6.2.4 Heparin-induced thrombocytopenia (HIT)

The cost of HIT was included in the model only for people receiving prophylaxis strategies that included LMWH. A weighted average cost for a HIT episode was then calculated based on a ratio of 75:25 for in-hospital to post-discharge diagnosis.

HIT events diagnosed in-hospital (pre-discharge) were assumed to be treated as an episode of thrombocytopenia with CC score 0-1 (HRG code SA12K). The national unit cost for this episode is £395. For events diagnosed post-discharge, it was assumed that either a visit to the GP (£36 for a visit of 9.9 minutes long),[224]or the emergency department (£222),[250] will also be required, in a ratio of 1:1, in addition to the hospital admission episode cost. The cost of diagnostic tests (4T clinical scoring and immunoglobulin assay) was also included. The cost of completing 4T clinical scoring was assumed to be that of 5 minutes of a registrar's time (costed at £60 per hour; £5.1 for 5 minutes). The cost of an immunoglobulin assay was £6, the national average unit cost of an immunology test (HRG code DAPS06). Hence, the total cost of visits and diagnosis was calculated to be an extra £134.3 for post-discharge diagnosis of HIT and the total cost would be £530. Hence, the weighted average cost of a HIT event in the model was £463.

For individuals who are successfully treated, no other costs were included. However, for those who develop new thrombosis, major bleeding or amputation; event-specific costs were also included. For a **new thrombosis**, the cost was calculated as the average of the cost of managing a symptomatic proximal DVT and that of managing a PE. For a **major bleeding**, the average cost of GI bleeding with and without intervention was used (£1,632). The cost of an **amputation** event was based on the NHS Schedule for Reference Costs 2015-2016 unit costs for amputation of single limb with CC scores 0-9 and 10+ (HRG codes YQ22A and YQ22B, weighted average of non-elective short, non-elective long and elective inpatient stay) to be £10,300.

P.1.3.6.3 Markov model Health states (> 90 days post-operatively

P.1.3.6.3.1 Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

For chronic thromboembolic pulmonary hypertension (CTEPH) we derived a yearly cost for first and subsequent years post diagnosis. We have estimated the cost of CTEPH by adding together the cost of diagnosis and treatment for year one and ongoing treatment for subsequent years. The diagnosis and treatment pathway was based on the European Society of Cardiology and European Respiratory

Society guidelines (2015),[332] NHS England clinical commissioning policy for targeted therapies for use in pulmonary hypertension in adults,[911] and a published analysis of an international registry of newly diagnosed patients with CTEPH.[245] This was supplemented by the guideline committee's expert input.

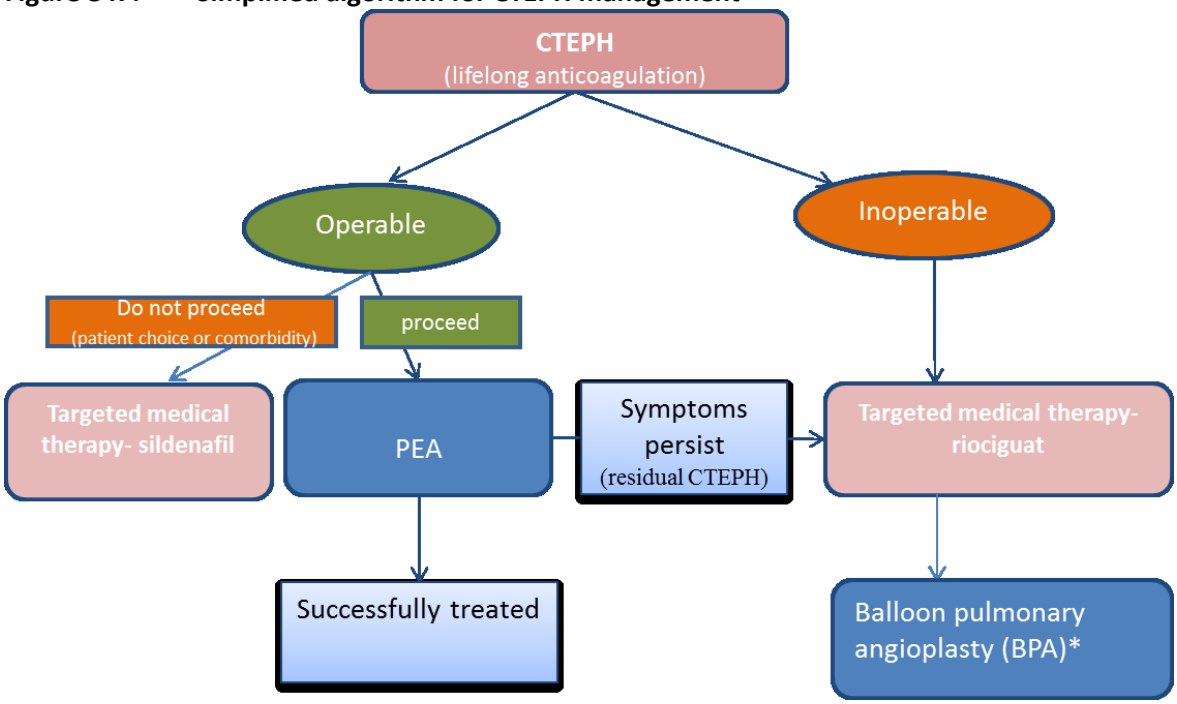
Diagnosis: The detailed costing of diagnosing CTEPH is presented in **Table 301.** It was based on the algorithm recommended by the European Society of Cardiology and European Respiratory Guidelines (2015) and the guideline committee's expert opinion. [332]

Table 301: Costs of diagnosing CTEPH

Item	% of patients	Resource used	units	unit cost	source
Clinical examination	100%	GP visit	1	£36	PSSRU 2016[224], 9.9 minutes.
	100%	Outpatient visit- Non-consultant led	1	£63	NHS Reference Costs 2015-2016 (non-consultant led respiratory medicine outpatient visit; service code 340) [250]
V/Q scan	100%	Diagnostic imaging-Outpatient	1	£274	NHS Reference Costs 2015-2016 (weighted average cost of of Lung Ventilation or Perfusion Scan, 18 years and under and 19 years and over; HRG codes: RN18A, RN18B)[250]
Referral/ outpatient visit	100%	Outpatient visit-consultant led	1	£192	NHS Reference Costs 2015-2016 (consultant led respiratory medicine outpatient visit; service code 340)[250]
CTPA	100%	Diagnostic imaging-Outpatient	1	£104	NHS Reference Costs 2015-2016 (weighted average cost of Computerised Tomography Scan of one area, with post contrast only, 19 years and over and 18 years and under; HRG codes RD21A and RD21B)[250]
Right heart catheterisation	100%	Test	1	£1,051	NHS Reference Costs 2015-2016 (weighted average cost of "Standard Cardiac Catheterisation with CC Score 0-1 to 10-12"; HRG codes EY43B to EY43F [Day cases]) [250]
Pulmonary angiogram/ angiography	20%	Test	1	£1,477	NHS Reference Costs 2015-2016 (weighted average cost of "Percutaneous Transluminal Angioplasty, including Stenting, of Intracranial or Extracranial Blood Vessel"; HRG codes YA10Z to YA 12Z) [250]
MRI pulmonary angiogram	80%	Test	1	£135	NHS Reference Costs 2015-2016 (weighted average cost of "Magnetic Resonance Imaging Scan"; HRG codes : RD01A, RD01B, RD02A, RD02B, RD03Z) [250]
			Total	**£2,123**	

Management: A simplified management algorithm was also constructed and costed based on the aforementioned sources (See **Figure 847**). In this algorithm, all patients with CTEPH were considered to continue long-term anticoagulation. Patients are assessed for operability and those considered operable (60%) would undergo pulmonary endarterectomy (PEA) surgery. Patients who are inoperable or continue to have residual symptoms after surgery and those who refuse surgery would receive targeted medical therapy in accordance with the Clinical Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults,[911] in addition to supportive therapy. New York Heart Association (NYHA) functional classification class I-II patients are assumed to receive supportive therapy only (39%).[245]

Figure 847: Simplified algorithm for CTEPH management



Abbreviations: BPA: Balloon pulmonary angioplasty CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy.

a) *Based on the European Society of Cardiology and European Respiratory Society guidelines (2015),[332] NHS England clinical commissioning policy for targeted therapies for use in pulmonary hypertension in adults,[911] and a published analysis of an international registry of newly diagnosed patients with CTEPH[245] supplemented by the guideline committee's expert input.*

b) **Not commissioned by the NHS.*

Anticoagulation: The cost of anticoagulation was calculated based on prescribing warfarin sodium tablets in a dose of 5mg on average. The annual cost of warfarin was thus calculated to be £10.66. Additionally, the annual cost of anticoagulation clinics, prothrombin time (once at the start of treatment) and INR testing were included. According to the BNF; INR testing is recommended to be undertaken daily or on alternate days in early days then less frequently and at least every 12 weeks after that, however; according to the committee, in clinical practice it is likely to be less frequently [3 to 4 days after a dose change] hence its cost might be an over-estimate. The total costs were £152.4 in year 1 and £28.1 in subsequent years. The costs of anticoagulation clinic visits were £42.3 for the first visit and £24.9 for subsequent follow-up visits.

Table 302: Costs of anticoagulation prescribing and management

category	Y1	Y2+
Warfarin (a)	£10.66	£10.66

category	Y1	Y2+
Monitoring tests (b)	£152.43	£28.05
Follow-up (c)	£315.87	£107.77
Total	**£478.96**	**£146.48**

Abbreviations: Y1: year 1; Y2+: years 2 to life time

(a) Average daily dose 5 mg (prescribed as 5mg tablets, 28 tablets per pack at an average price of £.82)

(b) PT once at the start, INR testing daily or alternate days in early days then less frequently and at least every 12 weeks. Source: British National Formulary[458]

(c) Y1 once a month, Y2 once every 12 weeks)

Pulmonary endarterectomy: the cost of the PEA operation was based on the costs provided by Papworth hospital, The UK's only designated PEA centre. This was reported to be £23,579.

Targeted medical therapy: According to the Clinical Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults,[911] patients with potentially operable CTEPH, those unsuitable for surgery due to co-morbidity and those who refuse surgery would be started on monotherapy with generic sildenafil (an oral phosphodiesterase type 5 inhibitors (PDE5I)), while patients with residual CTEPH post-PEA would routinely be prescribed the newly licensed soluble guanylate cyclase stimulator; riociguat. Balloon pulmonary angioplasty (BPA) might also be offered to some CTEPH patients, however; it is not currently funded by the NHS.

The yearly cost of each of the treatment options available for patients with CTEPH and the percentage of patients receiving each option in the year of diagnosis (Y1) and thereafter (Y2+) are presented in **Table 303**. These percentages were based on the NHS Clinical Commissioning Policy for year 1 and on data from the analysis of the international registry data in Delcroix 2016.[245] The number and costs of outpatient visits required for those prescribed riociguat are presented in **Table 304.** In practice; patients may not need so many follow up appointments and up titration in dose every 2 weeks can be done at home in a telephone consultation with nurse. For people prescribed sildenafil in year 1, the frequency of outpatients visits is assume to be once every 12 weeks. In Years 2+, follow-up for both drugs would occur at the same frequency (once every 12 weeks).

Based on these costs; and the percentage of total cost of both drug treatments and outpatient visits are in year 1 is £7,527 and in years 2+ is £19,212.

Table 303: Targeted medical therapy costs for patients with CTEPH in the first and subsequent years after diagnosis

Class	Drug	Annual drug cost (a)	% of patients	
			Year 1	Year 2 + (b)
Phosphodiesterase type 5 inhibitors (PDE5I)		**£154**	**87% (a)**	**28%**
	Sildenafil generic (for dose escalation 25-100mg three times daily)	£154		
Endothelin receptor antagonist (ERAs)/ Soluble guanylate cyclase stimulator		**£25,168(c)**		**39%**
	Bosentan (62.5mg – 125mg twice daily)	£23,500		
	Ambrisentan (5-10mg once daily)	£23,500		
	Macitentan (10mg once daily)	£27,672		
	Riociguat (dose as per titration – usually 2.5mg three times daily)(d)	£26,000	**13.1% (a)**	
Intravenous prostanoids		**£35,300 (d)**	**0.0%**	**3%**
	epoprostenol (dose titrated to response)	£35,000		
	Iloprost (5micrograms up to 9-times daily)	£35,600		
Dual Therapy		**£25,322**	**0.0%**	**30%**

Class	Drug	Annual drug cost (a)	% of patients	
			Year 1	Year 2 + (b)
	Sildenafil +ERA (e)	£25,322		
Total cost			**£3,527**	**£18,575**

(a) Source: Clinical Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults.[911] Not including home care costs.
(b) Source: Published analysis of an international registry of newly diagnosed patients with CTEPH.[245]
(c) Average of the annual costs of all ERAs.
(d) Average annual cost of IV prostanoids.
(e) According to the commissioning policy; dual therapy will only be funded in combinations involving a PDE5I unless there are exceptional circumstances.

Table 304: Outpatient visits for patients with residual CTEPH post-PEA surgery starting on riociguat

Year	Weeks	frequency	First/Follow-up	Unit cost	Total cost outpatient visits
1	2	every 2 weeks	First	£191.54 (a)	£191.54
1	2	every 2 weeks	Follow-up	£146.23 (b)	£146.23
1	2	every 2 weeks	Follow-up	£146.23 (b)	£146.23
1	2	every 2 weeks	Follow-up	£146.23 (b)	£146.23
1	44	every 4 weeks	Follow-up	£146.23 (b)	£1,618.09
Total-Y1					**£2,239**
Total-Y2	**52**	**every 12 weeks**	**Follow-up**	**£146.23** (b)	**£634**

(a) NHS Schedule for reference costs 2015-2016[250]; "Respiratory medicine" Service code 340; weighted average of HRG codes for outpatient first visit (HRG codes WF01B, WF01D, WF02B, WF02D)
(b) NHS Schedule for reference costs 2015-2016[250]; "Respiratory medicine" Service code 340; weighted average of HRG codes for outpatient follow-up visit (HRG codes WF01A, WF01C, WF02A, WF02C)

Supportive therapy: According to Schweikert 2015 and the guideline committee's expert opinion ;[871] the main supportive therapy currently used is diuretics in 59% of patients and supplemental oxygen in only 25%. Based on CG92, the diuretic used was assumed to be furosemide at an average dose of 40 mg per day; with an annual cost of £9.

Primary and secondary care resources: The associated with primary and secondary care resource use were included. The utilisation of these resources varied according to the functional class.

For NYHA class II, one outpatient visit and one day ward assessment were included annually at a cost of £147 (consultant led, follow-up visit, respiratory medicine; service code 340) and £332 (heart failure or shock, HRG code EB03A; Day case), respectively. For NYHA class III and IV; 1 outpatient visit and 2 day ward assessment visits. Repeated hospitalisation (4 episodes per year) were also included for NYHA class IV at a unit cost of £2,849 (heart failure or shock, HRG code EB03A; elective inpatient). A weighted average cost was calculated for the three functional classes based on the proportion of each class among CTEPH patients, as reported in Schweikert 2014. [871] The total cost of primary and secondary care resources used are presented in **Table 305**.

Table 305: Primary and secondary care resource use costs by NYHA class

Functional class	% of patients (a)	outpatient visits (b)	day ward assessment (b)	Hospital admissions (b)	outpatient visit unit cost (c)	day ward assessment unit cost (d)	Admission unit cost (e)	total cost
II	27%	1	1	0	£146	£332	£3,144	£478
III	59%	1	2	0				£810
IV	14%	1	2	4				£13,385

Functional class	% of patients (a)	outpatient visits (b)	day ward assessment (b)	Hospital admissions (b)	outpatient visit unit cost (c)	day ward assessment unit cost (d)	Admission unit cost (e)	total cost
Total cost								£2,481

Abbreviations: NYHA: New York Heart Association

a) Schweikert 2014 [871]

b) Guideline committee expert opinion

c) NHS Schedule for Reference Costs 2015-2016[250]. "Respiratory medicine" Service code 340; weighted average of HRG codes for consultant –led outpatient follow-up visit (HRG codes WF01A, WF01C, WF02A, WF02C)

d) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average of HRG codes for Day case, "Heart failure or shock" with CC 0-3 to 14+. HRG codes EB03A, EB03B, EB03C, EB03D and EB03E.

e) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average of HRG codes for elective inpatient, "Heart failure or shock" with CC 0-3 to 14+. HRG codes EB03A, EB03B, EB03C, EB03D and EB03E.

P.1.3.6.3.2 Post-thrombotic syndrome

In the case of **post-thrombotic syndrome** (PTS) we used a US-based study[153] that calculated the cost of managing PTS according to severity and year after diagnosis. This study has been used in TA157[675] and a recent UK HTA study[983]. We converted the costs to UK pounds using OECD purchasing power parity (PPP) calculator and inflated these to 2015-2016 UK pounds using the PSSRU hospital & community health services (HCHS) index.[224] Based on these estimates, the cost of managing mild/moderate PTS in the first and subsequent years are £841 and £342, respectively. The cost of managing severe PTS is the first and subsequent years are £3,824 and £1,680, respectively (see **Table 306**).

Table 306: Costs of managing post-thrombotic syndrome

	Reported cost (2000 US$)	Converted to 2000 UK£ (a)	Inflation index(b)	Inflated to 2015/16
mild-to-moderate PTS- year 1	$839	£533	1.576	£841
mild-to-moderate PTS- year 2+	$341	£217		£342
Severe PTS- years 1	$3,817	£2,427		£3,824
Severe PTS- years 2+	$1,677	£1,066		£1,680

(a) Converted using OECD purchasing power parity (PPP) calculator. [715]

(b) Source: PSSRU 2016.[224]

P.1.3.6.3.3 Disabled- post stroke

The cost of stroke management in the long term was based on the costs reported in NICE guideline CG144 "VTE management and thrombophilia testing". [668] The costs reported were adjusted for inflation using the PSSRU hospital & community health services (HCHS) index (see **Table 307**).[224] An average of the cost per patient in dependent and independent states was then used in the model. This was £17,374 in year 1 and £8,140 in subsequent years.

Table 307: Costs of managing people with haemorrhagic stroke in the first and subsequent years

	Cost (95% CI) (a)	Source
Cost of stroke per patient in the first year –dependent state	£29,776 (£22,332 to £37,220)	NICE VTE management and thrombophilia testing guideline (CG144), Appendix H[668]
Cost of stroke per patient in the first year –independent state	£4,971 (£3,729 to £6,214)	NICE VTE management and thrombophilia testing guideline (CG144), Appendix H[668]
Cost of stroke per patient for subsequent years – dependent state	£15,108 (£880 to £18,885)	NICE VTE management and thrombophilia testing guideline (CG144), Appendix H[668]

	Cost (95% CI) (a)	Source
Cost of stroke per patient for subsequent years – independent state	£1,172 (£880 to £1,465)	NICE VTE management and thrombophilia testing guideline (CG144), Appendix H[668]

a)Values from CG144 updated using an inflator index = 1.11 (from year 2010/2011 to year 2015/2016) calculated from PSSRU 2016 using the Hospital and Community Health Services Pay and Prices Index.[224]

P.1.3.6.3.4 Amputated- post HIT

The cost for individuals who were amputated post-HIT in the long term was based on the costs reported in NICE guideline CG147 "lower limb peripheral arterial disease".[667] The costs reported were adjusted for inflation using the PSSRU hospital & community health services (HCHS) index.[224] The cost per patient in year 1 was £31,259 and in subsequent years £25,987.

P.1.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in the long-term Markov part of the model by cross referencing the cohorts age as a respective risk factor for mortality. Baseline utility was also time dependent and was conditional on the number of years after entry to the model.

Patients start in cycle 0 in the health state corresponding to the end state of the decision tree part of the model. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities from the life tables and CTEPH mortality.

Transition probabilities for DVT, PE and MB were calculated based on the results of systematic review and NMAs conducted for the guideline, detailed in Appendix M of the full guideline.

PTS and CTEPH incidence rates were converted into transition probabilities for the respective cycle length (1 year in the base case) before inputting into the Markov model. These conversions were done using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t* *t*=time over which probability occurs (2 years)
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (1 year)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in states other than death in the model (1 year) was weighted by a utility value that is dependent on the time spent in the model and the utility value at the point of entry to the Markov model in Cycle 0. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

P.1.5 Sensitivity analyses

A number of one-way sensitivity analyses were undertaken to assess the parameter uncertainty of the model. These are listed in **Table 308.**

Table 308: List of one-way sensitivity analyses

	description	Base case input value	Alternative value for sensitivity analysis
SA1	Cost effectiveness threshold	£20,000	£30,000
SA2	Discount rate for costs and QALYs	3.5%	1.5%
SA3	Prophylaxis duration	Based on the RCTs included in the DVT NMA	based on summary of product characteristics (SmPC)
SA4	Cohort starting age	eTHR: 68.7 years (a) eTKR: 69.3 years (a)	40 years
SA5	Cohort body weight	NJR cohort mean body weight(a)	Cohort body weight distribution calculated based on the NJR cohort BMI distribution (a) and average height for a UK male (1.75m) and female (1.62 m) (b)
SA6	All costs +10%	See section P.1.3.6	Costs increased by 10%
SA7	All costs -10%	See section P.1.3.6	Costs decresed by 10%
SA8	Timing of VTE and MB events	Based on committee expert opinion	Based on data from Warwick 2007[993]
SA9	Rate VTE recurrence at 90 days after : Treated DVT PE	Assumption based on committee opinion 0% 0%	Calculated based on data from TA245 and TA354 manufacturer submissions. 2.74% 0.26%
SA10	Costs of pharmacological prophylaxis	Calculated assuming no wastage	Calculated taking possible wastage into account
SA11 (c)	Risk of DVT when using LMWH (std/std) followed by aspirin for the eTHR population	Calculated using the odds ratio from the PE network 0.05%	Calculated using the odds ratio from Anderson 2013 for the outcome Proximal DVT 3.68%

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

(a) Source: National Joint Registry[109]

(b) Source: ONS [708]

(c) Only for the eTHR population

P.1.6 Model validation

The model was developed in consultation with the Committee; model structure, inputs and results were presented to and discussed with the Committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of many of the model calculations.

P.1.7 Estimation of cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost-effective if:
- ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost-effective if:
- Highest net benefit

Results are also presented graphically where total costs and total QALYs for each strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

P.1.8 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[676] sets out the principles that Committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several interventions, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

P.2 Results

P.2.1 eTHR

P.2.1.1 Base case

The results of the probabilistic base case analysis for the eTHR population are presented in **Table 309** and in the cost-effectiveness plane in **Figure 848.** These show that the most effective option, with the highest mean gain in QALYs over lifetime per person, was the combined prophylaxis with LMWH (standard dose, standard duration) for 10 days followed by aspirin 100 mg for 28 days (10.293 discounted QALYs gained; 95% CI: 8.02 to 12.00). It was followed closely by LMWH (std,extd)+ AEs (10.288; 95% CI: 8.02 to 12.00). The most costly option was aspirin (standard duration), with mean discounted cost of £1,687 (95% CI: £157 to £4,039) per person. The least costly prophylaxis strategy was AES with mean discounted cost per person of £299 (95% CI: £102 to £793) followed by LMWH (standard, std) +aspirin (extd) with mean discounted cost of £311 (95% CI: £148 to £1437).

Based on these results, the most cost-effective prophylaxis strategy, with the highest NMB, was LMWH (std,std) + aspirin (extd) with mean INMB vs LMWH (stand, std)+AEs of £530 (95% CI: -£784 to £1,103). It also had the highest probability of being the most cost effective option (72%). Other interventions which have a positive mean INMB when compared with LMWH (std, std)+AEs are: LMWH (std,extd)+ AEs (mean £36; 95% CI: -£745 to £484) and AES (mean £5; 95% CI: -£2,106 to £781). However, compared to no prophylaxis, all interventions except aspirin (standard duration), foot pump and AES (above knee) have positive INMB.

Among the mechanical prophylaxis interventions; AEs seemed to be more cost effective compared to IPCD and foot pumps, ranking 3rd (95% CI: 1 to 14) when length was unspecified. However, above knee AES had negative INMB compared to no prophylaxis and ranked in the 14th place.

The DOACs (Rivaroxaban, apixaban and dabigatran) were dominant compared to no prophylaxis but were dominated by the model comparator (LMWH [standard dose, standard duration] +AES). Of the three DOACs, rivaroxaban was cost-effective compared to apixaban with an ICER of £12,242 per QALY gained both rivaroxaban and apixaban were dominant (more effective and less costly) compared to dabigatran.

The disaggregated costs and health outcomes presented in **Table 310** and **Table 311** show that the strategies that resulted in the lowest number of VTE events are LMWH (std,std)+aspirin (extd) and LMWH (std,extd) + AES (8 [95%: 0 to 55] and 34 [95% CI: 5 to 116] per 1000 persons; respectively). The highest number of VTE events was seen with the no prophylaxis strategy (491 per 1000 (95% CI: 146 to 953).

The number of surgical site bleeding events was highest for fondaparinux+ AES (51 per 1000 [95% CI: 8 to 187]) followed by dabigatran with 44 per 1000 [95% CI: 6 to 160] (see **Table 310**). Aspirin (std duration) was associated with the highest number of PE, PTS and CTEPH events (373, 60 and 11 per 1000 respectively).

The breakdown of costs for all prophylaxis strategies is presented in **Table 311** and is in line with the results for health outcomes. The cost of the prophylaxis itself was highest for LMWH (std,extd)+ AEs (£419 per person); driven by the high administration and monitoring costs for an extended duration.

P.2.1.2 Sensitivity analyses

The one-way sensitivity analyses (SAs) were all run deterministically. The results of the SAs show that the most cost-effective option remained the same in all except when the mean age of the cohort was

reduced to 40 years; where it dropped to the second rank and LMWH (std,std) + AES became the most cost effective.

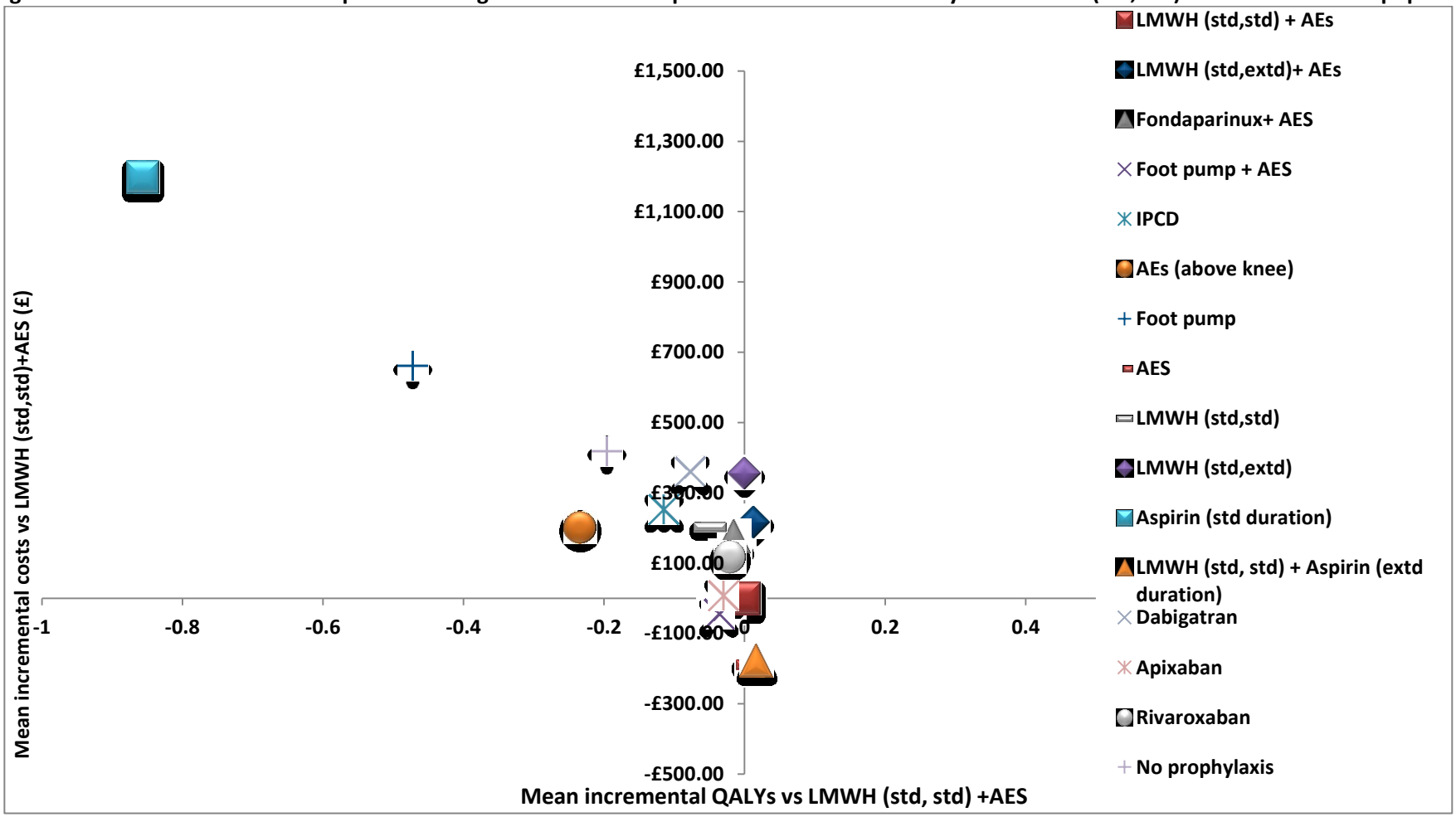
Table 309: Results of the base case probabilistic analysis for the eTHR population

Intervention	Mean discounted QALYs (95% CI)	Mean Discounted Costs (95% CI)	Incremental QALYs vs LMWH+ AEs (95% CI)	Incremental costs vs LMWH+ AEs (95% CI)	Mean INMB at £20K (95% CI)	Probability most CE option (a)	Rank (95% CI)
LMWH (std,std) + AEs	**10.28** (8.01 to 11.98)	**£489** (£350 to £832)	**0.000** (0.000 to 0.000)	**£0** (£0 to £0)	**£0** (£0 to £0)	0.1%	**4** (3, 11)
LMWH (std,extd)+ AEs	**10.29** (8.02 to 12.00)	**£706** (£509 to £1,376)	**0.013** (-0.004 to 0.030)	**£217** (-£42 to £694)	**£36** (-£745 to £484)	0.6%	**2** (2, 12)
Fondaparinux+ AES	**10.26** (7.98 to 11.96)	**£665** (£336 to £1,563)	**-0.015** (-0.112 to 0.013)	**£176** (-£92 to £800)	**-£478** (-£2,618 to £278)	0.2%	**6** (3, 15)
Foot pump + AES	**10.24** (7.99 to 11.94)	**£445** (£209 to £926)	**-0.036** (-0.182 to 0.012)	**-£44** (-£329 to £398)	**-£684** (-£3,930 to £478)	0.6%	**9** (2, 15)
IPCD	**10.16** (7.86 to 11.91)	**£742** (£255 to £1,968)	**-0.115** (-0.681 to 0.011)	**£253** (-£246 to £1,455)	**-£2,550** (-£14,733 to £396)	0.1%	**12** (4, 15)
AEs (above knee)	**10.04** (7.35 to 11.93)	**£691** (£119 to £3,765)	**-0.234** (-2.197 to 0.027)	**£202** (-£424 to £3,310)	**-£4,873** (-£46,725 to £861)	13.2%	**14** (1, 16)
Foot pump	**9.80** (6.96 to 11.77)	**£1,150** (£161 to £4,054)	**-0.472** (-2.681 to 0.015)	**£661** (-£344 to £3,578)	**-£10,104** (-£57,043 to £590)	1.4%	**15** (2, 16)
AES	**10.27** (8.01 to 11.97)	**£299** (£102 to £793)	**-0.009** (-0.103 to 0.022)	**-£189** (-£460 to £261)	**£5** (-£2,106 to £781)	8.4%	**3** (1, 14)
LMWH (std,std)	**10.23** (7.95 to 11.94)	**£691** (£375 to £1,413)	**-0.048** (-0.283 to 0.009)	**£202** (-£44 to £767)	**-£1,162** (-£6,266 to £197)	0.0%	**10** (6, 13)
LMWH (std,extd)	**10.27** (7.98 to 11.98)	**£844** (£528 to £1,582)	**0.000** (-0.070 to 0.025)	**£356** (£24 to £954)	**-£361** (-£2,042 to £349)	0.1%	**5** (4, 13)
Aspirin (std duration)	**9.42** (6.50 to 11.59)	**£1,687** (£157 to £4,039)	**-0.856** (-3.179 to 0.009)	**£1,198** (-£390 to £3,610)	**-£18,312** (-£66,988 to £479)	0.7%	**16** (2, 16)
LMWH (std, std) + Aspirin (extd duration)	**10.29** (8.02 to 12.00)	**£311** (£148 to £1437)	**0.018** (0.003 to 0.036)	**-£178** (-£548 to £781)	**£530** (-£784 to £1,103)	72.0%	**1** (1, 11)
Dabigatran	**10.20** (7.93 to 11.94)	**£849** (£319 to £1,957)	**-0.077** (-0.465 to 0.010)	**£360** (-£122 to £1,331)	**-£1,903** (-£10,144 to £254)	0.0%	**11** (5, 15)
Apixaban	**10.25** (7.96 to 11.97)	**£497** (£163 to £1,588)	**-0.030** (-0.270 to 0.022)	**£8** (-£302 to £895)	**-£598** (-£6,089 to £632)	2.2%	**8** (2, 14)
Rivaroxaban	**10.25** (7.97 to 11.97)	**£606** (£227 to £1,452)	**-0.021** (-0.190 to 0.019)	**£117** (-£234 to £814)	**-£529** (-£4,385 to £514)	0.4%	**7** (2, 13)
No prophylaxis	**10.08** (7.80 to 11.82)	**£908** (£297 to £2,185)	**-0.196** (-0.885 to -0.008)	**£419** (-£195 to £1,677)	**-£4,336** (-£19,297 to -£95)	0.0%	**13** (10, 16)

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

(a) Calculated at cost effectiveness threshold of £20,000 per QALY gained.

Figure 848: Cost-effectiveness plane showing the results of the probabilistic base case analysis vs LMWH (std, std) + AES for the eTHR population



Abbreviations: AEs: anti-embolism stockings; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; INMB: incremental net monetary benefit; LMWH: low molecular weight heparin; QALYs: quality-adjusted life-years; std: standard

Table 310: Health outcomes per 1000 for each prophylaxis strategy - eTHR population

Intervention	Short-term health outcomes (n [95% CI])							Long-term health outcomes (n [95% CI])	
	Symptomatic DVTs	Sympt Proximal DVT	Asymptomatic DVTs	PEs	Total VTEs	Surgical site bleeding	Total Deaths	PTS	CTEPH
LMWH (std,std) + AEs	**9** (8 to 11)	**8** (6 to 9)	**46** (44 to 48)	**7** (6 to 7)	**62** (61 to 64)	**28** (7 to 83)	**1** (1 to 3)	**7** (6 to 8)	**0** (0 to 0)
LMWH (std,extd)+ AEs	**6** (1 to 19)	**5** (1 to 16)	**27** (4 to 96)	**1** (0 to 9)	**34** (5 to 116)	**29** (2 to 131)	**0** (0 to 2)	**4** (1 to 13)	**0** (0 to 0)
Fondaparinux+ AES	**20** (7 to 42)	**17** (6 to 35)	**98** (36 to 204)	**12** (1 to 52)	**130** (52 to 263)	**51** (8 to 187)	**2** (0 to 11)	**14** (6 to 30)	**0** (0 to 2)
Foot pump + AES	**25** (3 to 81)	**21** (3 to 68)	**122** (16 to 388)	**22** (3 to 87)	**169** (35 to 486)	**13** (2 to 49)	**5** (0 to 19)	**19** (4 to 54)	**1** (0 to 3)
IPCD	**56** (10 to 134)	**47** (8 to 111)	**275** (49 to 634)	**53** (2 to 299)	**383** (79 to 858)	**13** (2 to 49)	**11** (0 to 62)	**43** (9 to 99)	b (0 to 9)
AEs (above knee)	**16** (2 to 58)	**14** (1 to 48)	**80** (8 to 278)	**106** (0 to 909)	**203** (16 to 996)	**13** (2 to 49)	**23** (0 to 202)	**26** (2 to 138)	**3** (0 to 26)
Foot pump	**17** (1 to 73)	**14** (1 to 61)	**84** (5 to 363)	**213** (1 to 980)	**314** (20 to 1078)	**13** (2 to 49)	**44** (0 to 243)	**41** (2 to 152)	**6** (0 to 30)
AES	**20** (1 to 91)	**16** (1 to 76)	**97** (4 to 440)	**11** (1 to 49)	**127** (11 to 539)	**13** (2 to 49)	**2** (0 to 11)	**14** (1 to 58)	**0** (0 to 2)
LMWH (std,std)	**34** (6 to 93)	**28** (5 to 78)	**168** (29 to 451)	**25** (2 to 128)	**227** (48 to 573)	**28** (7 to 83)	**5** (0 to 27)	**26** (6 to 65)	**1** (0 to 4)
LMWH (std,extd)	**32** (3 to 100)	**27** (3 to 83)	**158** (17 to 482)	**4** (0 to 32)	**194** (22 to 589)	**29** (2 to 131)	**1** (0 to 6)	**21** (2 to 65)	**0** (0 to 1)
Aspirin (std duration)	**10** (2 to 32)	**8** (1 to 26)	**49** (8 to 156)	**373** (3 to 995)	**433** (34 to 1066)	**10** (8 to 12)	**79** (1 to 288)	**60** (4 to 155)	**11** (0 to 31)
LMWH (std, std) + Aspirin	**1** (0 to 8)	**1** (0 to 7)	**6** (0 to 42)	**1** (0 to 6)	**8** (0 to 55)	**22** (0 to 190)	**0** (0 to 1)	**1** (0 to 6)	**0** (0 to 0)
Dabigatran	**48** (4 to 136)	**40** (4 to 113)	**233** (21 to 649)	**37** (1 to 204)	**317** (42 to 830)	**44** (6 to 160)	**8** (0 to 43)	**36** (5 to 93)	**1** (0 to 6)
Apixaban	**7** (0 to 30)	**6** (0 to 26)	**33** (2 to 145)	**21** (0 to 131)	**61** (6 to 252)	**42** (4 to 173)	**4** (0 to 28)	**7** (1 to 32)	**1** (0 to 4)
Rivaroxaban	**35**	**29**	**171**	**13**	**219**	**36**	**3**	**24**	**0**

Intervention	Short-term health outcomes (n [95% CI])							Long-term health outcomes (n [95% CI])	
	Symptomatic DVTs	Sympt Proximal DVT	Asymptomatic DVTs	PEs	Total VTEs	Surgical site bleeding	Total Deaths	PTS	CTEPH
	(4 to 110)	(3 to 92)	(19 to 527)	(0 to 88)	(28 to 651)	(4 to 138)	(0 to 18)	(3 to 73)	(0 to 3)
No prophylaxis	**68** (16 to 139)	**57** (13 to 115)	**335** (80 to 669)	**88** (8 to 384)	**491** (146 to 953)	**13** (2 to 49)	**18** (1 to 82)	**56** (16 to 112)	**3** (0 to 12)

Abbreviations: AEs: anti-embolism stockings; CTEPH: chronic thromboembolic pulmonary hypertension; DVT: deep vein thrombosis; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; PE: pulmonary embolism; PTS: post thrombotic syndrome;.std: standard; VTE: venous thromboembolism.

Table 311: Cost breakdown for each prophylaxis strategy per person - eTHR population

Intervention	Prophylaxis costs	VTE costs (95% CI)	All Bleeding costs (95% CI)	CTEPH costs (95% CI)	PTS costs (95% CI)	Post-amputation Costs (95% CI)	Total costs (a) (95% CI)
LMWH (std,std) + AEs	**£169**	**£11** (£10 to £11)	**£210** (£72.8 to £554)	**£19** (£15.4 to £23)	**£60** (£52 to £69)	**£20** (£13 to £27)	**£489** (£350 to £833)
LMWH (std,extd)+ AEs	**£419**	**£4** (£5.1 to £13)	**£217** (£39 to £847)	**£4.2** (£3 to £26)	**£32** (£5 to £107)	**£28** (£18 to £39)	**£706** (£509 to £1,376)
Fondaparinux+ AES	**£115**	**£20** (£5.8 to £59)	**£375** (£92 to £1,248)	**£32** (£2 to £144.5)	**£124** (£49 to £254)	**£0.00** (£0.00 to £0.00)	**£665** (£336 to £1,563)
Foot pump + AES	**£91**	**£32** (£7.3 to £103)	**£99** (£23 to £334)	**£60** (£7 to £228)	**£163** (£34 to £456)	**£0.00** (£0.00 to £0.00)	**£445** (£209 to £926)
IPCD	**£68**	**£75** (£11.3 to £327)	**£99** (£23 to £334)	**£129** (£4 to £654.5)	**£371** (£78 to £847)	**£0.00** (£0.00 to £0.00)	**£742** (£255 to £1,968)
AEs (above knee)	**£50**	**£112** (£1.6 to £908)	**£99** (£23 to £334)	**£211** (£36 to £1,502)	**£219** (£15 to £1,183)	**£0.00** (£0.00 to £0.00)	**£691** (£119 to £3,765)
Foot pump	**£60**	**£218** (£4.7 to £978)	**£99** (£23 to £334)	**£420** (£3.5 to £1,632)	**£354** (£19 to £1,300)	**£0.00** (£0.00 to £0.00)	**£1,150** (£161 to £4,054)
AES	**£31**	**£19** (£2.5 to £61.7)	**£99** (£23 to £334)	**£30** (£2 to £136)	**£121** (£11 to £498)	**£0.00** (£0.00 to £0.00)	**£299** (£102 to £793)
LMWH (std,std)	**£138**	**£39** (£7.6 to £140)	**£210** (£72.8 to £554)	**£66** (£5 to £311)	**£218** (£47 to £555)	**£20** (£13 to £27)	**£691** (£375 to £1,413)
LMWH (std,extd)	**£387**	**£17** (£2.4 to £54.7)	**£217** (£39 to £847)	**£12** (£0.1 to £87)	**£181** (£21 to £551)	**£28** (£18 to £39)	**£845** (£528 to £1,582)
Aspirin (std duration)	**£0.24**	**£374** (£7.2 to £989)	**£98** (£82 to £119)	**£702** (£8 to £1,687)	**£512** (£34 to £1,322)	**£000** (£000 to £000)	**£1,687** (£157 to £4,034)
LMWH (std, std) + Aspirin	**£115**	**£1.4** (£2 to £9)	**£163** (£11 to £1,225)	**£3** (£0 to £18)	**£7.5** (£0.01 to £54)	**£20** (£13 to £27)	**£311** (£148 to £1,437)
Dabigatran	**£80**	**£55.6** (£7.5 to £227)	**£316** (£75.5 to £1,048)	**£93** (£4 to £487)	**£305** (£42 to £795)	**£0.00** (£0.00 to £0.00)	**£849** (£319 to £1,957)
Apixaban	**£59**	**£23.5** (£1.5 to £132.6)	**£298** (£56.5 to £1,139)	**£53** (£1 to £321)	**£63** (£6.5 to £270)	**£0.00** (£0.00 to £0.00)	**£497** (£163 to £1,588)
Rivaroxaban	**£74**	**£27** (£3.4 to £105)	**£265** (£58.6 to £907)	**£34** (£0.4 to £225)	**£206** (£28 to £629)	**£0.00** (£0.00 to £0.00)	**£606** (£227 to £1,452)
No prophylaxis	**£0**	**£115** (£26 to £416)	**£99** (£23 to £334)	**£213** (£24 to £810)	**£481** (£140 to £957)	**£0.00** (£0.00 to £0.00)	**£908** (£297 to £2,185)

Abbreviations: AEs: anti-embolism stockings; CI: confidence interval; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; std: standard; VTE: venous thromboembolism; CTEPH: chronic thromboembolic pulmonary hypertension; PTS: post thrombotic syndrome.

a) May not exactly equal the sum of the components due to rounding.

P.2.2 eTKR

P.2.2.1 Base case

The results of the probabilistic base case analysis for the eTKR population are presented in **Table 312** and on the cost-effectiveness plane in **Figure 849**. These showed that the most effective option, with the highest mean gain in QALYs over lifetime per person, was foot pump (9.814 [95% CI: 7.86 to 11.58] discounted QALYs gained). This was followed closely by aspirin with a mean of 9.809 (95% CI: 7.86 to 11.58) and LMWH (std,std)+AES with a mean of 9.807 (95% CI: 7.86 to 11.58). The most costly option was fondaparinux+ AES, with mean discounted costs £904 (95% CI: £358 to £3,016). The least costly prophylaxis strategy was aspirin, with mean discounted costs of £187 (95% CI: £118 to £304).

Based on these results, the most cost-effective prophylaxis strategy, with the highest NMB, was foot pump with mean INMB vs LMWH (stand, std)+AEs of £353 (95% CI: -£101 to £665) followed by aspirin with mean INMB of £281 (95% CI: -£195 to £703). However, the results show considerable uncertainty where the most cost-effective option (foot pump) rank having a 95% CI of 1 to 10 and a probability of being the most cost-effective of only 18%. The only interventions with positive INMB when compared with LMWH (std, std)+AEs were foot pump, aspirin and combination of foot pump + AES. Compared to no prophylaxis, though, all interventions had a positive INMB except dabigatran.

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

The disaggregated health outcomes and costs for all prophylaxis strategies are presented in **Table 313** and **Table 314.** These show that rivaroxaban had the lowest number of VTE events (60 per 1000 persons [95% CI: 14 to 211]). The number of surgical site bleeding events was highest for fondaparinux+ AES (79 per 1000 [95% CI: 2 to 411]) followed by rivaroxaban (16 per 1000 [95% CI: 1 to 67]). The “no prophylaxis” strategy was associated with the highest number of PTS events (23 per 1000 [7 to 81]), Dabigatran had the highest number of PE events (51 per 1000 [0 to 644]).

The disaggregate costs were in line with the results for health outcomes. The cost of the prophylaxis itself was highest for LMWH (std,extd) at £356 per person.

P.2.2.2 Sensitivity analyses

One-way SAs were run deterministically. The optimal strategy (foot pump) remained the same in all SAs. Dabigatran was the least cost effective option in all SAs.

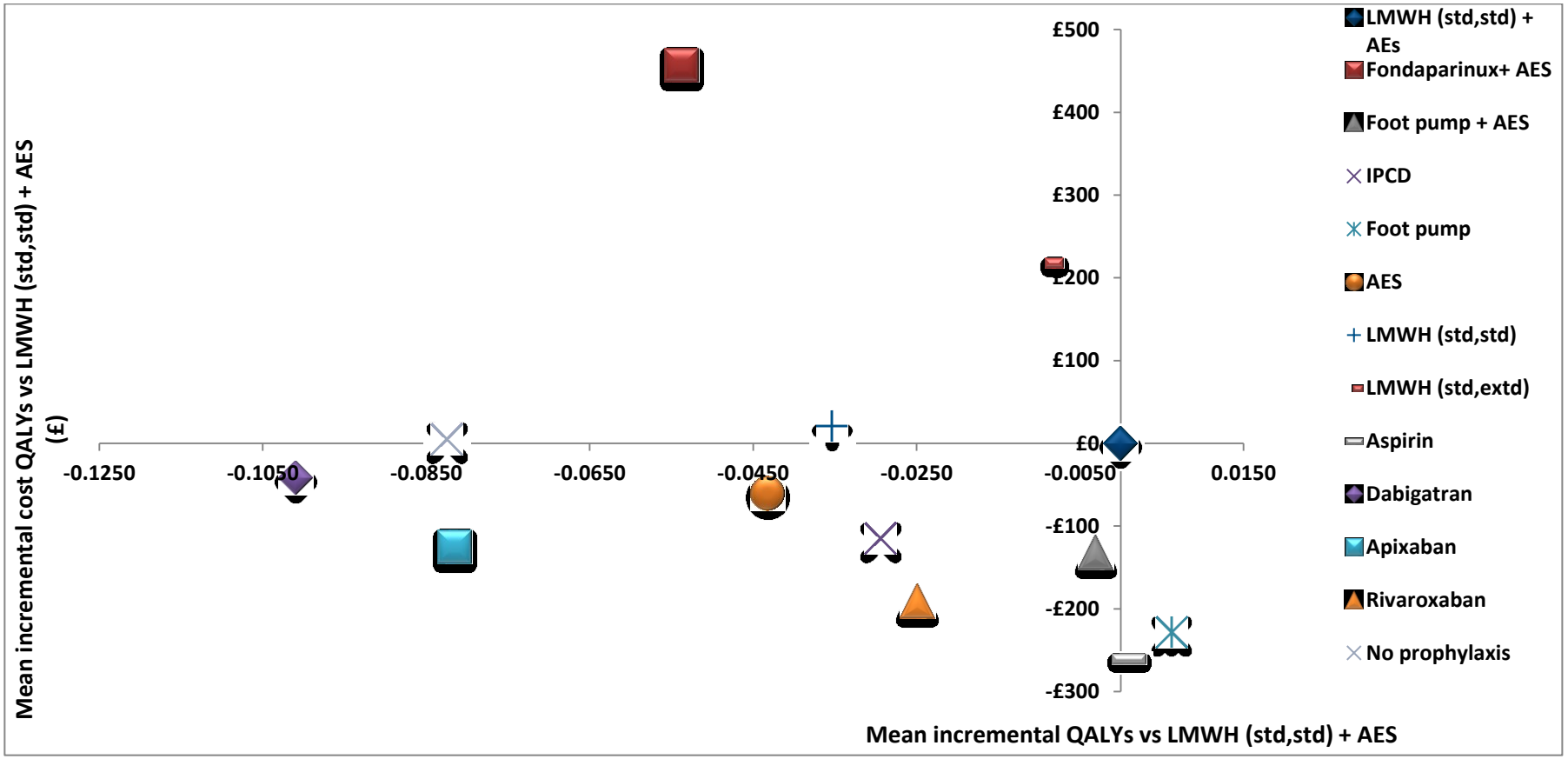
Table 312: Results of the base case probabilistic analysis vs LMWH (std, std)+AES for the eTKR population

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

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

(a) Calculated at cost effectiveness threshold of £20,000 per QALY gained.

Figure 849: Cost-effectiveness plane showing the results of the probabilistic base case analysis- eTKR population



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

Table 313: Health outcomes breakdown per 1000 for each prophylaxis strategy - eTKR population

Intervention	Short-term health outcomes (n (95% CI))							Long-term health outcomes (n(95% CI))	
	Symptomatic DVT	Sympt Proximal DVT	Asymptomatic DVT	PE	Total VTE	Surgical site bleeding	Total Deaths	PTS	CTEPH
LMWH (std,std) + AEs	**6** (5 to 8)	**1** (0 to 2)	**134** (132 to 136)	**4** (4 to 5)	**144** (143 to 146)	**9** (1 to 32)	**1** (0 to 2)	**8** (6 to 11)	**0** (0 to 0)
Fondaparinux+ AES	**6** (2 to 13)	**1** (0 to 3)	**121** (36 to 261)	**10** (2 to 25)	**136** (46 to 284)	**79** (2 to 411)	**2** (0 to 6)	**8** (3 to 16)	**0** (0 to 1)
Foot pump + AES	**9** (4 to 15)	**2** (0 to 4)	**181** (91 to 311)	**6** (3 to 11)	**195** (101 to 333)	**12** (1 to 51)	**1** (0 to 3)	**10** (5 to 19)	**0** (0 to 0)
IPCD	**10** (3 to 19)	**2** (0 to 5)	**202** (66 to 405)	**19** (0 to 175)	**230** (71 to 495)	**12** (1 to 51)	**4** (0 to 35)	**13** (4 to 38)	**1** (0 to 5)
Foot pump	**4** (0 to 12)	**1** (0 to 3)	**79** (11 to 243)	**3** (0 to 9)	**85** (14 to 259)	**12** (1 to 51)	**1** (0 to 2)	**5** (1 to 14)	**0** (0 to 0)
AES	**13** (6 to 22)	**3** (1 to 6)	**285** (144 to 465)	**24** (0 to 203)	**323** (158 to 567)	**12** (1 to 51)	**5** (0 to 39)	**18** (8 to 48)	**1** (0 to 6)
LMWH (std,std)	**4** (1 to 9)	**1** (0 to 2)	**89** (30 to 195)	**21** (0 to 232)	**114** (33 to 337)	**9** (1 to 32)	**4** (0 to 44)	**8** (2 to 37)	**1** (0 to 7)
LMWH (std,extd)	**4** (1 to 10)	**1** (0 to 2)	**76** (18 to 204)	**8** (0 to 49)	**88** (19 to 238)	**10** (0 to 68)	**2** (0 to 10)	**5** (1 to 16)	**0** (0 to 1)
Aspirin	**7** (2 to 17)	**1** (0 to 4)	**149** (39 to 367)	**5** (1 to 12)	**160** (45 to 390)	**9** (8 to 11)	**1** (0 to 3)	**9** (2 to 20)	**0** (0 to 0)
Dabigatran	**4** (1 to 10)	**1** (0 to 2)	**88** (27 to 199)	**51** (0 to 644)	**142** (32 to 722)	**11** (1 to 45)	**11** (0 to 127)	**12** (2 to 98)	**2** (0 to 19)
Apixaban	**2** (1 to 6)	**0** (0 to 1)	**51** (15 to 121)	**44** (0 to 568)	**97** (18 to 606)	**8** (0 to 35)	**9** (0 to 102)	**9** (1 to 85)	**1** (0 to 16)
Rivaroxaban	**2** (1 to 5)	**0** (0 to 1)	**42** (11 to 104)	**16** (0 to 163)	**60** (14 to 211)	**16** (1 to 67)	**3** (0 to 34)	**4** (1 to 24)	**0** (0 to 5)
No prophylaxis	**15** (6 to 27)	**3** (1 to 7)	**328** (132 to 565)	**41** (0 to 429)	**385** (151 to 781)	**12** (1 to 51)	**8** (0 to 87)	**23** (7 to 81)	**1** (0 to 13)

Abbreviations: AEs: anti-embolism stockings; CTEPH: chronic thromboembolic pulmonary hypertension; DVT: deep vein thrombosis; eTKR: elective total knee replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; PE: pulmonary embolism; PTS: post thrombotic syndrome;.std: standard; VTE: venous thromboembolism.

Table 314: Cost breakdown for each prophylaxis strategy per person - eTKR population

Intervention	Prophylaxis costs	VTE costs (95% CI)	All Bleeding costs (95% CI)	CTEPH costs (95% CI)	PTS costs (95% CI)	Post-amputation costs (95% CI)	Total costs (a) (95% CI)
LMWH (std,std) + AEs	**£142**	**£6** (£5 to £6)	**£93** (£32 to £260)	**£13** (£10 to £15)	**£67** (£52 to £99)	**£101** (£69 to £142)	**£448** (£364 to £613)
Fondaparinux+ AES	**£128**	**£11** (£3 to £26)	**£671** (£140 to £2,769)	**£27** (£7 to £72)	**£67** (£25 to £139)	**£0.00** (£0.00 to £0.00)	**£904** (£358 to £3,016)
Foot pump + AES	**£91**	**£8** (£4 to £13)	**£109** (£30 to £371)	**£17** (£8 to £33)	**£91** (£46 to £165)	**£0.00** (£0.00 to £0.00)	**£315** (£208 to £590)
IPCD	**£42**	**£21** (£0.9 to £177)	**£109** (£30 to £371)	**£45** (£0.001 to £448)	**£116** (£31 to £337)	**£0.00** (£0.00 to £0.00)	**£333** (£133to £1,246)
Foot pump	**£60**	**£4** (£0.8 to £10)	**£109** (£30 to £371)	**£8** (£1.0 to £25)	**£40** (£7 to £118)	**£0.00** (£0.00 to £0.00)	**£219** (£119 to £473)
AES	**£31**	**£27** (£2 to £203)	**£109** (£30 to £371)	**£59** (£0.2 to £485)	**£161** (£66 to £401)	**£0.00** (£0.00 to £0.00)	**£387** (£167 to £1,397)
LMWH (std,std)	**£111**	**£21** (£0.4 to £231)	**£93** (£32 to £260)	**£49** (£0.001 to £572)	**£67** (£14.5 to £328)	**£101** (£69 to £142)	**£468** (£287 to £1,563)
LMWH (std,extd)	**£356**	**£9** (£0.2 to £50)	**£107** (£21 to £511)	**£19** (£0.00 to £130)	**£46** (£8 to £137)	**£103** (£68 to £150)	**£666** (£508 to £1,302)
Aspirin	**£0.49**	**£6** (£2 to £14)	**£92** (£70 to £130)	**£14** (£3 to £36)	**£74** (£21 to £178)	**£0.00** (£0.00 to £0.00)	**£187** (£118 to £304)
Dabigatran	**£34**	**£51** (£0.4 to £640)	**£106** (£32 to £34)	**£111** (£0.002 to £1,322)	**£104** (£14 to £867)	**£0.00** (£0.00 to £0.00)	**£406** (£100 to £2,987)
Apixaban	**£23**	**£44** (£0.2 to £564)	**£80** (£23 to £254)	**£97** (£0.002 to £1,157)	**£79** (£8 to £753)	**£0.00** (£0.00 to £0.00)	**£322** (£69 to £2,624)
Rivaroxaban	**£25**	**£16** (£0.16 to £162)	**£139** (£38 to £470)	**£37** (£0.00 to £388)	**£39** (£6 to £214)	**£0.00** (£0.00 to £0.00)	**£256** (£82 to £1,206)
No prophylaxis	**£0**	**£44** (£2 to £429)	**£109** (£30 to £371)	**£97** (£0.05 to £962)	**£203** (£64 to £701)	**£0.00** (£0.00 to £0.00)	**£453** (£137 to £2,281)

Abbreviations: AEs: anti-embolism stockings; eTKR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; std: standard; VTE: venous thromboembolism; CTEPH: chronic thromboembolic pulmonary hypertension; PTS: post thrombotic syndrome.

a) May not exactly equal the sum of the components due to rounding.

P.3 Discussion

P.3.1 Summary of results

For eTHR, the most cost-effective prophylaxis strategy, with the highest NMB, was LMWH (standard dose, standard duration) + aspirin (extended duration) with mean INMB £530 (95% CI: -£784 to £1,103). It also had the highest probability of being the most cost-effective option (72%). Where parentral options are not acceptable or contraindicated; rivaroxaban would be the most cost-effective prophylaxis option. Of the mechanical prophylaxis options considered in the analysis; AES-based strategies appeared to be the more cost effective option compared to IPCDs and foot pumps. However, it was not possible to directly compare the length of the AES (knee vs thigh length) in terms of cost effectiveness as there were no effectiveness data for the knee-length stockings to allow its inclusion in this analysis.

For eTKR, foot pump was found to be the most cost-effective option with mean INMB of £353 (95% CI: -£101 to £665) however, with only 18% probability of being the most cost-effective option. It was followed by aspirin with mean INMB of £281 (95% CI: -£195 to £703). The incremental analysis vs LMWH (std, std)+AES also showed that dabigatran ranked worse than no prophylaxis. rivaroxaban dominated both apixaban and dabigatran for this population. Of the mechanical prophylaxis options; foot pump or IPCD were found to be more cost-effective than AES.

P.3.2 Comparisons with published studies

To our knowledge, this analysis is the first to include all interventions for primary prevention of VTE in eTHR and eTKR that are currently available in the NHS; including mechanical, pharmacological and combination prophylaxis. It is also the first to account for outcomes such as the consequences of HIT including amputation; consequences of major bleeding including joint infections, wound haematoma and return to theatre. The model structure represented both the acute phase in the immediate post-operative period as well as the long term phase to life-time time horizon; using a Markov model to capture long-term consequences including PTS and CTEPH. It has been based on NMAs of the three main outcomes DVT, PE and major bleeding. These NMAs combined the evidence from the randomised controlled trials (RCTs) included in our clinical systematic review to obtain coherent estimates of relative effectiveness, for all the included interventions, to be used in the economic analysis.

A recent literature review of economic models of VTE prophylaxis in THR and TKR,[131] included economic evaluations published from 2008 to 2015 that compared anticoagulants; as pharmacological prophylaxis options.[257,272,273,351,620-622,638,651,797,833,1017,1018,1051] The source of efficacy data in most of the included studies was either a single trial or meta-analysis of two or more of the DOACs' phase-3 trials. The review authors concluded that, of the pharmacological options considered, the use of DOACs for primary prevention of VTE resulted in a small incremental QALY gain vs LMWH which may be too small to be clinically meaningful. They also concluded that out of the DOACs considered, rivaroxaban and apixaban were more cost effective than dabigatran. On the other hand, an earlier systematic review of economic evaluations of pharmacological prophylaxis published in 2010;[474] concluded that fondaparinux and extended duration LMWH appear to be cost-effective strategies. These two reviews, however, did not include studies that compared mechanical prophylaxis options or considered combinations of both mechanical and pharmacological prophylaxis.

Our systematic review of the published economic evidence identified 32 economic studies, in 35 publications, relating to THR and TKR. [41,103,104,125,149,228,234,257,267,269,352,354,374,381,587,620-622,638,666,670,675,677,678,766,793,797,801,833,919,921,985,1017,1018,1051] These included 3 NICE TAs, 2 evidence review group

[ERG] reports and the CG92 model for standard duration and post discharge prophylaxis. Also, 10 of these publications were previously included in CG46.[41,103,104,228,234,267,354,374,587,793]
Overall, published economic evaluations in eTHR and eTKR that compared VTE prophylaxis to no prophylaxis concluded that prophylaxis was a cost-effective intervention.[666,670] The choice of an optimum prophylaxis strategy, however, varied across studies and among countries. This is partly explained by the difference in the range of interventions included in each of these studies but also by the differences in acquisition costs and sources of effectiveness evidence. In accordance with Brockbank 2017 conclusion;[131] our analysis shows that the differences between the included interventions in terms of QALYs-gained is very small and the results are likely to be more sensitive to differences in costs.

The results also showed that out of the DOACs considered; rivaroxaban is the most cost-effective. In eTHR, rivaroxaban dominated dabigatran and was cost-effective compared to apixaban with an ICER of 12,242 per QALY-gained. This was in line with the results of TA170 where rivaroxaban was found to dominate dabigatran.[677] A recent analysis funded by the NIHR found that rivaroxaban dominated dabigatran and was cost-effective compared to apixaban with an ICER of £114 per QALY gained.[919] TA245 also found that dabigatran was dominated, apixaban was extendedly dominated and rivaroxaban had an ICER of £22,123 per QALY-gained compared to fondaparinux.[678] In eTKR, rivaroxaban dominated both apixaban and dabigatran. This was in line with the results of the economic models assessed as part of TA170 and TA245 and a more recent analysis funded by the NIHR.[677,678,919]

However; our analysis showed that LMWH in combination with AES is more cost effective than the DOACs. This is in accordance with the conclusion of another systematic review of economic evaluations of pharmacological prophylaxis published in 2010;[474] which concluded that fondaparinux and extended duration LMWH can be cost-effective strategies.

We have assumed no recurrence of VTE events following treatment. This was decided after discussion with the clinical experts in the guideline committee as it was felt that recurrence may not be related to the provoked VTE event that happens after the surgery and may be related to previous VTE events. Additionally, prevention of VTE recurrence is a primary outcome for the effectiveness of the VTE treatments used. As we have assumed that these treatments are 100% effective in our base case analysis; risk of recurrence was assumed to be 0%. This assumption might have underestimated the cost effectiveness of the interventions that were more effective in preventing PE and DVT. So, we tested this assumption in a one-way sensitivity analysis using data on rate of recurrence from TA245 and TA354 which reported rates of recurrence following treated DVT and PE. This sensitivity analysis did not result in any change in the ranking of the interventions for either of the two populations.

Additionally, due to lack of data on either DVT or PE outcomes for some interventions, an assumption still had to be made about the equivalence of relative effectiveness on the DVT and PE outcomes for these interventions. However, we have limited this only to instances where data was available for one of these outcomes but not for the other. However; as this assumption may have affected the results; we have tested it in sensitivity analyses. This was clearly a possibility in case of the eTKR analysis; where the relative effectiveness of foot pump, aspirin and foot pump + AES in relation to the PE outcome was assumed to be the same as their relative effectiveness obtained from the DVT NMA. This has resulted in a much lower PE rate for these interventions compared to all the others. Similarly, the relative effectiveness of LMWH (std, std)+ aspirin (extd duration) in relation to the DVT outcome for the eTHR population was based on its relative effectiveness obtained from the PE NMA. This assumption may have also affected the results. However, we tested this assumption in a sensitivity analysis using data on proximal DVT from the same trial that reported the PE data for this intervention (Anderson 2013)(SA10). This sensitivity analysis did not result in a change in the model results.

P.3.3 Limitations and interpretation

Our model was an update of the CG92 model; so we attempted to address the limitations of that model which were highlighted by the orthopaedic surgeons' community in a number of publications. One limitation was the use of relative effectiveness from the DVT NMA for the PE outcomes. In our analysis, we avoided making this assumption unless absolutely necessary; where the intervention was not included in the PE network. However, we have verified this assumption with the guideline committee and externally validated it using the observational data analysis that used NJR data;[450,451] where the ratio of the relative effectiveness of LMWH vs aspirin for the DVT outcome was found to be approximately the same as for the PE outcome (analysis available on request), supporting the assumption of proportionality of effectiveness for these two VTE outcomes.

Another issue was the lack of differentiation between proximal and distal DVT. We have addressed this issue by differentiating between the proximal and distal DVT for both symptomatic and asymptomatic events. We also allowed for different probabilities of progressing from each of these DVT outcomes to PTS; to acknowledge the fact that progression from treated and untreated DVT to PTS would be different. We emphasised the fact that asymptomatic DVT also does not have an impact on costs and outcomes in the short term as it is not diagnosed in practice and its only consequence in the model is its future progression to PTS. There was also a concern regarding the baseline risk used in the model which was based on data from the no prophylaxis arm in the RCTs. This was not felt to be reflective of current incidence of VTE with some trials dating back to the 70s, especially as practice has changed in terms of encouraging early mobilisation as well as the difference in surgical techniques. Based on this, we have used LMWH +AES as our model comparator and obtained its baseline risk data from observational cohort studies that used the UK NJR data.[450,451]

However, despite all our efforts; the results of this economic analysis are still highly uncertain; in particular for the TKR population. This reflects the uncertainty and imprecision of the NMA results that underpinned it due to the sparse data and small number of RCTs for each comparison in networks; particularly for the PE and MB outcomes. These imprecise estimates of cost effectiveness preclude defining a clear ranking of the included interventions in terms of their cost-effectiveness. This is a reflection of the state of the collective body of evidence in this clinical area and it is not correct to try to address this by using only direct, pairwise meta-analyses or economic evaluations as this will simply ignore the majority of the evidence available.

Another limitation of this analysis is that the relative safety of aspirin compared to LMWH was based on an observational cohort analysis based on NJR data. [450,451] This was due to the lack of any randomised controlled trials that report major bleeding outcomes for aspirin in these populations. However, as the data for MB from trials are likely to be imprecisely estimated, due to the rarity of these events; it was felt that this would be an appropriate source of relative effectiveness for a safety outcome.

P.3.4 Generalisability to other populations or settings

The results of this analysis have been largely based on epidemiological and cost data specific to England including the cohort characteristics which were based on data from the NJR. Additionally, the interventions included in the analysis were true to current UK clinical practice. This may limit the generalisability to other populations and settings. However, the relative effectiveness estimates were based on comprehensive systematic reviews and NMAs that did not restrict the inclusion of studies to specific countries. Hence, the results relating to the health outcomes are likely to be generalisable. Additionally, this analysis has been undertaken from a UK NHS and PSS perspective; hence its results might not be generalizable beyond these settings. The population modelled also represents a cohort whose characteristics might be different from eTHR and eTKR cohorts in other countries.

P.3.5 Conclusions

In people undergoing elective total hip replacement e(THR), VTE prophylaxis appears to be cost effective compared to no prophylaxis. A strategy consisting of LMWH (standard dose) for 10 days followed by aspirin for 28 days was the most cost effective. This result was robust to changes in the model input parameters. LMWH-based strategies that use extended duration LMWH or its combination with AES are more cost-effective compared to LMWH standard duration alone or in combination with AES. Rivaroxaban was found to be the most cost-effective of the DOACs considered in this analysis.

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

Evidence statements

One original cost-utility analysis found that, in people admitted for elective total hip replacement surgery, the following interventions were cost-effective (having positive incremental net monetary benefit [INMB]) compared to LMWH (standard dose, standard duration) +AEs: LMWH (standard dose, standard duration) + aspirin (extended duration) (INMB £530); LMWH (standard dose, extended duration)+ AEs (INMB £36) and AES (INMB: £5). This analysis was assessed as directly applicable with minor limitations.

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

P.3.6 Implications for future research

Future research need to focus on assessing the relative safety of the different prophylaxis strategies. No studies were found to report usable data on the side effects of the mechanical prophylaxis strategies. Additionally, the evidence available for the safety outcomes of the pharmacological interventions is only based on RCTs of short duration and, given the rarity of the events, the results are highly uncertain as the trials are not powered to detect differences in these secondary outcomes. Given the increased interest in the use of real world evidence (RWE) and the availability of large registry and audit data reporting these outcomes in the post-marketing phase; more research should focus on developing methodologies to assess the relative safety of the pharmacological prophylaxis interventions using these observational data.

Our results showed that aspirin is likely to be a cost effective prophylaxis strategy for eTKR. For eTHR it was not found to be cost effective. This was primarily based on a single, dated RCT that does not reflect current practice. Given that anecdotal evidence from current practice and evidence from large observational studies contradict the findings from this study and suggest that aspirin is likely to be more effective as a prophylaxis strategy in eTHR than what has been seen in that study; it would be highly informative if its relative effectiveness and safety in this population is assessed in a well-conducted and adequately powered RCT. Aspirin is a very cheap intervention that can be highly cost-effective if effectiveness and safety can be established in such an RCT.

Appendix Q: Unit costs

Q.1 Mechanical prophylaxis

Table 315: Costs of mechanical prophylaxis strategies

Component of mechanical prophylaxis	Cost(a) (b)
Anti-embolism stockings (per pair)	
knee length/below knee	£4.07
Thigh length	£7.75
Full length	£9.16
Graduated Compression stockings (GCS) (per pair)	
Calf/knee-high/below knee	£25.36
Thigh length	£42.68
Intermittent pneumatic compression (sleeves)	
IPC sleeve with vascular refill detection-knee length	£26.50
IPC sleeve with vascular refill detection-Thigh length	£34.36
Foot impulse devices (pads)	
Foot impulse device (pads)	£44 (c)

Abbreviations: GCS: graduated compression stocking; IPC: intermittent pneumatic compression.

(a) Average of all available sizes (small to XXXL for AES and small to XL for IPCD)

(b) Source: NHS Supply chain catalogue 2015[685]

(c) Source: CG92, adjusted for inflation to 2015-2016 prices using inflation index from the Curtis 2016.[224,666]

Table 316: Costs of mechanical prophylaxis options

Component of mechanical prophylaxis	Average cost of all sizes (a)	Average price of Large/XL, XXL and XXL sizes only (a)
Anti-embolism stockings (2 pairs per patient)		
knee length/below knee	£4.04 (per pair)	£4.27 (per pair)
Thigh length	£7.30 (per pair)	£8.87 (per pair)
Full length	£9.14 (per pair)	£9.21 (per pair)
Intermittent pneumatic compression (sleeves) (1 pair per patient)		
IPC sleeve with vascular refill detection-knee length	£26.51 (per pair)	£37.80 (per pair)
IPC sleeve with vascular refill detection-Thigh length	£33.29 (per pair)	£37.05 (per pair)

(a) Source: NHS Supply chain catalogue 2015[685]

Table 317: Cost of fitting and monitoring of mechanical prophylaxis

Prophylaxis method	Nurse time required for fitting (a)	Cost of fitting (b)	Nurse time required daily for monitoring (a)	Daily cost of monitoring (b)
Stockings	10 minutes	£6	5 minutes	£3
Intermittent compression	5 minutes	£3	5 minutes	£3

devices				

(a) Committee estimate
(b) Calculated based on hospital-based nurse band 5 cost of £36 per hour [224]

Q.2 Pharmacological prophylaxis

Table 318: Unit costs of routinely used pharmacological prophylaxis options

Drug	Preparation	Mg/ units	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Units/ day	Mg/ day	Cost/ day (£)	Cost/ month (£)
Heparin sodium	solution for injection-vials	5000 IU	10	£11.20 (a)	£1.12	3	n/a	£3.36	£102.20
Enoxaparin sodium	solution for injection pre-filled syringes	40 mg	10	£30.27 (b)	£3.03	n/a	40	£3.03	£92.07
Dalteparin sodium	Solution for injection-pre-filled syringes	5000 IU	10	£28.23 (c)	£2.82	1	n/a	£2.82	£85.87
Tinzaparin sodium	Solution for injection-pre-filled syringes	3500 IU	10	£27.71 (c)	£2.77	1	n/a	£2.77	£84.28
Tinzaparin sodium	Solution for injection-pre-filled syringes	4500 IU	10	£35.63 (c)	£3.56	1	n/a	£3.56	£108.37
Fondaparinux sodium	solution for injection pre-filled syringes	2.5 mg/ 0.5ml	10	£43.95 (c)	£4.40	1	2.5	£4.4	£134
Rivaroxaban	tablets	10 mg	30	£63.00 (a)	£2.10	1	10	£2.10	£63.88
Apixaban	tablets	2.5 mg	20	£19.00 (c)	£0.95	2	2.5	£1.90	£57.79
Dabigatran etexilate	capsules	110 mg	60	£65.90 (a)	£1.10	1	110 mg	£1.1	£33
Dabigatran etexilate	capsules	110 mg	60	£65.90 (a)	£1.10	2	220 mg	£2.2	£67
Dabigatran etexilate	capsules	150 mg	60	£65.90 (a)	£1.10	1	150 mg	£1.1	£33

Drug	Preparation	Mg/ units	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Units/ day	Mg/ day	Cost/ day (£)	Cost/ month (£)
Dabigatran etexilate	capsules	75 mg	60	£65.90 (a)	£1.10	1	75 mg	£1.1	£33
Aspirin	tablets	300 mg	32	£3.35 (a)	£0.10	1 (d)	300 mg (d)	£0.1	£3

(a) Source: eMIT/CMU December 2015.[207]
(b) Source: NHS Drug Tariff August 2016. [682]
(c) Source: British National Formulary (BNF) June 2016.[458]
(d) Aspirin doses considered in the protocol are up to 300mg, so the dose presented here is the maximum possible prophylactic dose per day.

Table 319: Cost of pharmacological prophylaxis options for people with body weight > 150 Kg

Class	Drug	Preparation	Mg/ units	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Cost/ mg (£)	Units/ day	Mg/ day	Cost/ day (£)	Cost/ month (£)
Low molecular weight heparin (LMWH)											
	Enoxaparin sodium	solution for injection pre-filled syringes	60 mg	10	39.26 (a)	£3.93	£0.07	2	120mg	£7.85	£239
	Dalteparin sodium	Solution for injection-pre-filled syringes	7,500 IU	10	£42.34 (b)	£4.23	£0.001	2	n/a	£8.47	£258
	Tinzaparin sodium	Solution for injection-pre-filled syringes	8,000 IU	10	£47.60 (b)	£4.76	£0.001	2	n/a	£9.52	£290

(a) Source: NHS Drug Tariff August 2016.[682]
(b) Source: British National Formulary (BNF) June 2016.[458]

Table 320: Unit costs of pharmacological prophylaxis options by pre-pregnancy weight category

Pre-pregnancy weight	Drug	Preparation	Mg/ units	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Cost/ mg (£)	Units/ day (c)	Mg/ day	Cost/ day (£)	Cost/ month (£)
< 50kg											
	Enoxaparin sodium	solution for injection pre-filled syringes	20 mg/0.2ml	10	£20.86(a)	£2.09	£0.104	1	20mg	£2.09	£63.45
	Dalteparin sodium	Solution for injection-pre-filled syringes	2,500 IU	10	£18.58(b)	£1.86	£0.001	1	n/a	£1.86	£56.51
	Tinzaparin sodium	Solution for injection-pre-filled syringes	3,500 IU	10	£27.71(b)	£2.77	£0.001	1	n/a	£2.77	£84.28
50-90 Kg											
	Enoxaparin	solution for	40	10	£30.27(a)	£3.03	£0.076	1	40mg	£3.03	£92.07

Pre-pregnancy weight	Drug	Preparation	Mg/ units	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Cost/ mg (£)	Units/ day (c)	Mg/ day	Cost/ day (£)	Cost/ month (£)
	sodium	injection pre-filled syringes	mg/0.4ml								
	Dalteparin sodium	Solution for injection-pre-filled syringes	5,000 IU	10	£28.23(b)	£2.82	£0.001	1	n/a	£2.82	£85.87
	Tinzaparin sodium	Solution for injection-pre-filled syringes	3500 IU	10	£27.71 (b)	£2.77	£0.00	1	n/a	£2.77	£84.28
91-130 kg											
	Enoxaparin sodium	solution for injection pre-filled syringes	60 mg/0.6 ml	10	£39.26(a)	£3.93	£0.065	1	60 mg	£3.93	£119.42
	Dalteparin sodium	Solution for injection-pre-filled syringes	7,500 IU	10	£42.34(b)	£4.23	£0.001	1	n/a	£4.23	£128.78
	Tinzaparin sodium	Solution for injection-pre-filled syringes	3,500 IU	10	£27.71(b)	£2.77	£0.001	2	n/a	£5.54	£168.57
131–170 kg											
	Enoxaparin sodium	solution for injection pre-filled syringes	80 mg/0.8ml	10	£55.13(a)	£5.51	£0.069	1	80mg	£5.51	£167.69
	Dalteparin sodium	Solution for injection-pre-filled syringes	10,000 IU	5	£28.23(b)	£5.65	£0.001	1	n/a	£5.65	£171.73
	Tinzaparin sodium	Solution for injection-pre-filled syringes	4,500 IU	10	£35.63(b)	£3.56	£0.001	2	n/a	£7.13	£216.75

Pre-pregnancy weight	Drug	Preparation	Mg/ units	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Cost/ mg (£)	Units/ day (c)	Mg/ day	Cost/ day (£)	Cost/ month (£)
Prophylactic dose for women weighing 50-90 kg											
	Enoxaparin sodium	solution for injection pre-filled syringes	40 mg/0.4ml	10	£30.27(a)	£3.03	£0.076	2	80 mg	£6.05	£184.14
	Dalteparin sodium	Solution for injection-pre-filled syringes	5,000 IU	10	£28.23(b)	£2.82	£0.001	2	n/a	£5.65	£171.73
	Tinzaparin sodium	Solution for injection-pre-filled syringes	4,500 IU	10	£35.63(b)	£3.56	£0.001	2	n/a	£7.13	£216.75

(a) Source: NHS Drug Tariff August 2016. [682]
(b) Source: British National Formulary (BNF) June 2016. [458]
(c) Source: RCOG Green Top Guideline 2015.[827]

Table 321: Costs of administration and monitoring- pharmacological prophylaxis

Prophylaxis strategy	Tests required	Nurse time associated with administering and monitoring prophylaxis	frequency of administration per day in hospital	Cost of nurse time per injection	Cost of tests(a)
UFH (Heparin sodium)	Full blood count: baseline (plus the day after start if previous exposure to UFH) then alternate days from day 4-14 (b)	2-3 minutes per injection (c)	3	£1.83(c)	£48
LMWH	Full blood count: baseline then every 2-4 days until day 14 (b)	2-3 minutes per injection (c)	1	£1.83(c)	£ 51.79 (d)
Fondaparinux sodium	-	2-3 minutes per injection (c)	1	£1.83(c)	n/a

Prophylaxis strategy	Tests required	Nurse time associated with administering and monitoring prophylaxis	frequency of administration per day in hospital	Cost of nurse time per injection	Cost of tests(a)
Dabigatran etexilate	Baseline liver and renal function test	n/a	n/a	n/a	£12.95

(a) The tests were costed at £3 per test, the average for a haematology test, plus £3 phlebotomist cost (NHS Reference Costs 2015-2016). Where a range is specified, maximum number of tests was assumed.

(b) Based on estimates from CG92 and committee expert opinion (BCSH guideline and Keeling 2006[481]).

(c) Time per injection is based on committee estimate. Cost of administration in hospital is based on hospital-based nurse band 6 time at a cost of £44 per hour (source: Unit Costs of Health and Social Care 2016). Standard UK licensed dose and an average time per injection of 2.5 minutes were used for the calculation.

(d) Cost of tests calculated per week.

Appendix R: Research recommendations

High-priority research recommendations

R.1 Risk assessment

Research question: What is the accuracy of individual risk assessment tools in predicting the risk of VTE and risk of bleeding in people admitted to hospital?

Why this is important:

Risk assessment is mandatory for all people admitted or having day procedures in hospital. Since 2010 the National VTE Risk Assessment Tool has been widely used in the NHS to assess a person's risk of VTE. This tool has not been validated or tested against other tools to evaluate its diagnostic accuracy or effectiveness at correctly identifying people at risk of VTE. There is concern that the tool may not accurately identify those who are most likely to get VTE. According to national figures, over 70% of medical patients in the UK have prophylaxis when the National Tool has been used, with some trusts offering prophylaxis to over 90% of medical patients. Around 40% of medical patients have prophylaxis in largely US-based populations when other tools are used (although this may partially relate to different indications for hospital admission). It is not known if this means that the national tool identifies too many people or the other tools do not identify enough. The potential impact of giving unnecessary prophylaxis is that people may be at increased risk of bleeding and discomfort through repeated injections. There is also the potential for reducing the cost of thromboprophylaxis by better defining "at risk" populations, so that the number of those given thromboprophylaxis is reduced.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People admitted to hospital including: • Medical patients • Surgical and trauma patients • Pregnant women and women up to six weeks post-pregnancy Risk tool(s): Validation of risk tools in a UK population. Possible risk tools include (but are not limited to): • The National VTE Risk Assessment Tool • IMPROVE • Caprini risk assessment model • Trauma Embolic Scoring System (TESS) • Intermountain risk assessment model • Kucher score • Padua prediction score • Khorana score • Royal College of Obstetrics & Gynaecologists (RCOG) VTE risk assessment checklist Target condition(s): VTE, major bleeding Outcome(s): Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values)

	• Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) • Reclassification • Other statistical measures: for example, D statistic, R^2 statistic and Brier score
Importance to patients or the population	All NHS patients have the potential to develop VTE. VTE prophylaxis has the potential to cause harm to patients. Accurately identifying the patients most likely to develop VTE will help prevent VTE while avoiding giving unnecessary prophylaxis.
Relevance to NICE guidance	Since the original NICE guideline was published in 2010 (https://www.nice.org.uk/guidance/cg92/) the current guideline committee noted concerns that a lot of people may not need the prophylaxis they are being given.
Relevance to the NHS	Currently, there is a checklist known as the National VTE Risk Assessment Tool (http://webarchive.nationalarchives.gov.uk/20130123195034/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_088215) that has been used to determine whether people should get prophylaxis. However, while it details individual risk factors for VTE it leads to a high proportion of patients being given prophylaxis. For acute medically ill patients this equates to over 70% of all admissions. Other tools would only lead to around 40% of patients getting prophylaxis. According to a cost impact analysis conducted as part of the guideline development, this would mean a substantial cost saving. It would also mean that considerably less patients being at risk of possible side effects from un-necessary prophylaxis. It is not clear which tool would have the required level of specificity to identify these patients who will not go on to have a VTE event while minimising false negatives. .
National priorities	The National VTE Prevention Programme in England that was initiated in 2010 to reduce the incidence of VTE within a policy framework for VTE risk assessment together with guidance on appropriate prophylaxis. VTE is a considered a national priority with NHS England mandating data collection for risk assessment (https://www.england.nhs.uk/statistics/statistical-work-areas/vte/).
Current evidence base	While there are several published risk assessment tools for venous thromboembolism in a variety of populations none have been validated in an NHS population or compared to each other.
Equality	No known inequalities
Study design	Ideally prospective observational cohort design or randomised controlled trial.
Feasibility	It should be feasible as all patients are currently risk assessed. This research would only require them to pick a different tool to use.
Other comments	This was considered to be an important area for research when the original guideline was published in 2010 and a research recommendation was made to reflect this. However, research has yet to be commissioned. The current guideline committee believe this is a very important area for research as it affects all NHS patients admitted to hospital or visiting as day cases for medical or surgical procedures.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

R.2 Dose strategies for people who are obese

Research question: What is the clinical and cost effectiveness of weight-based dose-adjustment strategies of LMWH compared with fixed dose strategies of LMWH for preventing VTE in people

who are very obese (BMI over 35) who are admitted to hospital or having day procedures (including surgery and chemotherapy)?

Why this is important:

Obesity is on the rise in England. The prevalence of obesity increased by 11% between 1993 and 2014 (15% in 1993 and 26% in 2014),[401] which has resulted in more obese people being admitted to hospital. Obesity may as much as double a person's risk of developing hospital-acquired VTE, [225 ,653] therefore most obese people will need prophylaxis. There is much uncertainty about what dose to use and the clinical and cost-effectiveness of using weight-based dose-adjustment versus fixed-dose strategies. In current practice a higher than usual dose is gven but this may not be necessary, especially if the person has obesity-related liver disease. Several studies have reported effectiveness in terms of biological measures rather than clinical outcomes such as DVT and bleeding events. It is important that there is a clearer understanding of the effects that different dose strategies can have in terms of clinical outcomes. This is because they can directly influence the quality of life of obese people admitted to hospitals and help inform clinical decisions on patient care.

Criteria for selecting high-priority research recommendations

PICO question	Population:
	Adults and young people (16 years and older) who are very obese (BMI > 35) and who are:
	• Admitted to hospital
	• Having day procedures
	• Outpatients post-discharge
	
	Intervention(s):
	Pharmacological (fixed dose or weight adjusted dose):
	• Low molecular weight heparin (LMWH), licensed in UK:
	  ○ enoxaparin
	  ○ dalteparin
	  ○ tinzaparin
	• LMWH, licensed in countries other than UK:
	  ○ Bemiparin
	  ○ Certoparin
	  ○ Nadroparin
	  ○ Parnaparin
	  ○ Reviparin
	
	Comparison:
	• Fixed dose
	• Weight adjusted dose
	
	Outcome(s):
	Critical outcomes:
	• All-cause mortality (up to 90 days from hospital discharge)
	• Deep vein thrombosis (symptomatic and asymptomatic) (measured at 7-90 days from hospital discharge).
	• Pulmonary embolism (measured at 7-90 days from hospital discharge).
	• Major bleeding (measured at up to 45 days from hospital discharge).
	• Fatal PE (measured at 7- 90 days from hospital discharge).

	Important outcomes: • Clinically relevant non-major bleeding (measured at up to 45 days from hospital discharge) • Health-related quality of life (validated scores only)(measured at up to 90 days from hospital discharge) • Heparin-induced thrombocytopenia (HIT) (duration of study)
Importance to patients or the population	Knowing which dosing strategy is the most appropriate for obese people is very important. This would ensure that the most effective LMWH dosing strategy is used for optimum prophylactic anticoagulation to reduce risk of VTE and bleeding. Administration of VTE prophylaxis is often a decision based on weighing the risk of VTE and risk of bleeding. It is widely accepted that higher doses of LMWH can increase risk of bleeding. Some healthcare settings are using weight-adjusted doses of LMWH for people who are obese, doses that can be above standard prophylactic doses. This may potentially increase a patient's risk of bleeding even though there is no evidence that this may be clinically beneficial (there is also no evidence that it is clinically harmful).
Relevance to NICE guidance	Due to the lack of evidence in this topic area a clinical recommendation for this topic could not be made by the guideline committee. Answering this research question would ensure that future guidelines committees are equipped with essential data in regards to clinical and cost-effectiveness outcomes so that a recommendation can be made.
Relevance to the NHS	This research question is important in standardising clinical practice across the NHS as presently some hospitals use weight-adjusted dosing whereas others use fixed doses in people who are obese. There are different costs associated with the different dosing strategies; weight-adjusted doses may be more costly, a cost-effectiveness analysis to evaluate this potential cost-increase is vital. A change in practice to either one of the dosing strategies should not lead to any major changes logistically.
National priorities	The National VTE Prevention Programme in England that was initiated in 2010 to reduce the incidence of VTE within a policy framework for VTE risk assessment together with guidance on appropriate prophylaxis (http://webarchive.nationalarchives.gov.uk/+/http://www.dh.gov.uk/en/Publichealth/Healthprotection/Bloodsafety/VenousThromboembolismVTE/DH_113359. In order to contribute to this initiative, it is crucial that a dosing strategy is recommended for people who are obese. The NHS Outcomes Framework 2016-2017 [249] has highlighted 'deaths from VTE related events' as an area for improvement in reducing the incident of avoidable harm.
Current evidence base	No relevant studies have been identified that have compared fixed dose versus weight-adjusted dose, evaluating clinical outcomes and cost-effectiveness outcomes.
Equality	No known equalities issues. Note: LMWHs are porcine-derived products which may not be suitable for some patients due to religious reasons.
Study design	Ideally randomised controlled trial in a hospital setting with economic evaluation. Otherwise dose ranging non randomised studies would be helpful.
Feasibility	No feasibility concerns anticipated.
Other comments	None
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

R.3 Direct oral anticoagulants for people with lower limb immobilisation

Research question: What is the clinical and cost effectiveness of direct oral anticoagulants (DOACs) for preventing VTE in people with lower limb immobilisation?

Why this is important:

The Computerized Registry of Patients with Venous Thromboembolism (RIETE) Study, a multicentre prospective cohort study of 30,886 patients with acute VTE, estimated that 5.7% of VTE events were associated with lower limb immobilisation for non-major orthopaedic surgery. Estimates of DVT risk in people with lower limb immobilisation, based upon meta-analyses of trials comparing chemothromboprophyalxis with placebo, range between approximately 4% and 40%. Given that lower limb immobilisation following trauma or non-major orthopaedic surgery is so common the consequent burden of disease from VTE from this cause in the whole population is very considerable. For example, the annual incidence of ankle fracture is 187 per 100,000, translating to over 120,000 incident fractures per year in the UK. If 10% of these fractures are complicated by VTE then we might expect approximately 12,000 events per year only related to immobilisation following ankle trauma.

Despite this burden of ill-health no randomised studies comparing modern anticoagulants which are available in oral preparations, perhaps more suitable for outpatient treatments, with established treatments such as LMWH or fondaparinux were identified in the evidence review. The committee were unable to make a recommendation to consider oral anticoagulants for this patient group given this lack of evidence.

Criteria for selecting high-priority research recommendations

PICO question	Population:
	• Patients treated non-operatively for ankle fracture with immobilisation of the lower limb using plaster casts or orthoses
	Intervention(s):
	• DOAC for period of immobilisation (likely 45 days). Options include:
	  ○ Apixaban
	  ○ Rivaroxaban
	  ○ Dabigatran
	• LMWH for period of immobilisation (likely 45 days).
	Comparison:
	• No prophylaxis
	Outcome(s):
	• Measures of effectiveness
	  ○ Cause-specific mortality (assessed at 90 days)
	  ○ Pulmonary embolism (assessed at 90 days)
	  ○ DVT (assessed at 90 days post-operatively)
	  ○ Post-thrombotic syndrome severity (Villata Score assessed at one year)
	  ○ Quality of life (venous disease-specific QoL assessed at one year)
	• Measures of harm:
	  ○ Major bleeding (assessed at 45 days post-operatively)
	  ○ Clinically relevant non-major bleeding (to include surgical site bleeding) assessed at 45 days post-operatively

	• Resource use
	  ○ GP visits
	  ○ Hospital admissions
	  ○ Medication use

Importance to patients or the population	Current VTE prophylaxis guidance recommends LMWH or fondaparinux, both treatments which require daily injections. The quality of the evidence which supports this recommendation is assessed to be low or very low. Patients can reasonably expect future research to explore whether any prophylaxis is effective for this population, and if so whether an oral agent is clinically and cost effective in this setting.
Relevance to NICE guidance	Current VTE prophylaxis guidance recommends LMWH or fondaparinux, both treatments which require daily injections. These recommendations are based upon few, small trials which suggest that prophylaxis may be beneficial in this population. A definitive study of an oral anticoagulant suitable for outpatient use could substantially alter the guidance, both in terms of the provision of any prophylaxis at all and the specific agent used.
Relevance to the NHS	The RIETE Study, a multicentre prospective cohort study of 30 886 patients with acute VTE, estimated that 5.7% of VTE events were associated with lower limb immobilisation for non-major orthopaedic surgery. Estimates of DVT risk in patients with lower limb immobilisation, based upon meta-analyses of trials comparing chemothromboprophyalxis with placebo, range between approximately 4 and 40%. Given that lower limb immobilisation following trauma or non-major orthopaedic surgery is so common the consequent burden of disease from VTE from this cause in the whole population is very considerable. For example, the annual incidence of ankle fracture is 187 per 100,000; translating to over 120,000 incident fractures per year in the UK. If 10 per cent of these fractures are complicated by VTE then we might expect approximately 12,000 events per year only related to immobilisation following ankle trauma.
National priorities	The National VTE Prevention Programme in England that was initiated in 2010 to reduce the incidence of VTE within a policy framework for VTE risk assessment together with guidance on appropriate prophylaxis. The NHS Outcomes Framework 2016-2017 [249] has highlighted 'deaths from VTE related events' as an area for improvement in reducing the incident of avoidable harm.
Current evidence base	Eight trials have been conducted comparing LMWH with no prophylaxis, the majority of which are small. However, only a minority of these trials reported outcomes determined by the committee to be important in determining clinical effectiveness. The consequent lack of precision and risk of bias in these trials means that the quality of the evidence is assessed to be very low. There were no trials of modern DOACs in this population. There were no economic evaluations available for any comparisons. Given how common the use of lower limb immobilisation it is important to be able to determine a clinically and cost effective prophylaxis strategy.
Equality	LMWHs are porcine-derived products which may not be suitable for some patients due to religious reasons. The availability of other alternatives would address this issue.
Study design	A three-arm (DOAC, LMWH, no prophylaxis) individual patient-level randomised controlled trial with an associated economic evaluation.
Feasibility	Given that there is known heterogeneity amongst effect sizes across clinically diverse populations treated with lower limb immobilisation, it is reasonable to focus upon one large and homogenous population – ankle fracture. Irrespective of treatment these patients are all immobilised for a period of six weeks during fracture healing. In addition the likely confounders of operative management and weight-bearing status are easily described and can be controlled. The population sustaining ankle fracture in the UK is sufficiently large that a large multi-centre trial could be conducted relatively quickly and therefore

	without being unduly expensive (estimate 2 years across 30 centres). Clinical equipoise is clearly apparent with some units making local recommendations that differ from the NICE VTE prophylaxis guidance.
Other comments	It is likely that only NIHR would be able to fund such a trial which might reasonably be expected to find that prophylaxis is ineffective in this very low risk population such that any future study is likely to be commercially not viable.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

R.4 Aspirin prophylaxis for people with fragility fractures of the pelvis, hip or proximal femur

Research question: What is the clinical and cost effectiveness of aspirin alone versus other pharmacological and/or mechanical prophylaxis strategies (alone or in combination) for people with fragility fractures of the pelvis, hip or proximal femur?

Why this is important:

Fragility fractures are the greatest burden of musculoskeletal disease in hospitals in the UK. There are approximately 70,000 fragility hip fractures per year in England alone leading to 1.5 million bed days being used each year, which equates with the continuous occupation of over 4,000 NHS beds.

Current evidence supports a recommendation for prophylaxis with LMWH or fondaparinux. Both involve a subcutaneous injection for 28 days requiring either self-injection at home or a community nurse attending to deliver the injection. Patient adherence to treatment may be improved with an oral rather than injectable treatment.

A large but controversially reported trial[776] suggests that aspirin may be at least as effective as currently recommended treatments. However, because of methodological and reporting limitations the evidence for the effectiveness of aspirin alone is not clear. There is potentially a large cost saving if aspirin is clinically effective because it is very inexpensive.

Criteria for selecting high-priority research recommendations

PICO question	Population:
	• patients with lower limb fragility fractures of the hip
	Intervention(s):
	• aspirin alone (for 28-35 days)
	Comparison:
	• recommended standard of care
	  ○ LMWH alone (for 28-35 days)
	  ○ LMWH is overwhelmingly the treatment in use in UK hospitals due to the reduced cost compared with fondaparinux
	Outcome(s):
	• UK core outcome set for hip fracture,[399] particularly:
	• Measures of effectiveness
	  ○ All cause and cause-specific mortality (assessed at 90 days post-operatively)
	  ○ Pulmonary embolism (assessed at 90 days post-operatively)
	  ○ DVT (assessed at 90 days post-operatively)
	  ○ Quality of life (EQ-5D) (assessed at 120 days post-operatively)

	• Measures of harm:
	  ○ Major bleeding (assessed at 45 days post-operatively)
	  ○ Clinically relevant non-major bleeding (to include surgical site bleeding) assessed at 45 days post-operatively
	• Resource use
	  ○ Length of stay
	  ○ Readmission
	  ○ Return to premorbid residence

Importance to patients or the population	The current evidence is assessed to be at too great a risk of bias to be considered for the clinical guideline recommendation. However the PEP trial,[776] including more than 13,000 participants, does suggest that aspirin may be as clinically effective as LMWH. Patient adherence and satisfaction may be substantially improved with aspirin which is an oral preparation. Currently, both recommended drugs for prophylaxis require administer a subcutaneous injection administered by the patient themselves or a nurse attending the patient's residence.
Relevance to NICE guidance	Future VTE prophylaxis guidance would be able to definitively state whether aspirin is a clinical and/or cost effective method of prophylaxis. If aspirin were effective then a definitive study would fundamentally change the recommendation.
Relevance to the NHS	There are approximately 70,000 hip fractures each year in England.[828] A cheaper but effective prophylaxis strategy could potentially generate considerable cost savings for the NHS given the burden of this injury. VTE prophylaxis continues to be a controversial clinical question with many trauma and orthopaedic surgeons believing that aspirin is a suitable method of prophylaxis. Addressing this research question could help resolve this issue.
National priorities	The National VTE Prevention Programme in England that was initiated in 2010 to reduce the incidence of VTE within a policy framework for VTE risk assessment together with guidance on appropriate prophylaxis. The NHS Outcomes Framework 2016-2017 [249] has highlighted 'deaths from VTE related events' as an area for improvement in reducing the incident of avoidable harm.
Current evidence base	The evidence for aspirin was inconclusive. One of the larger trials conducted in this population was the PEP trial that was published in 2000, evaluating the use of aspirin. The committee noted that the PEP trial was a complex trial that included mixed interventions. The data reported include just over 50% of patients with either LMWH or UFH, and around 30% using stockings. It is not reported how many of these patients received both heparin and stockings, or who had aspirin alone or no prophylaxis at all. The study also reported a post hoc analysis for the combined outcome of pulmonary embolism and symptomatic DVT. This showed that a reduction in symptomatic VTE events using aspirin (plus or minus stockings) without the use of heparin and a reduction of symptomatic VTE events with stockings (plus or minus the use of heparin). The outcomes of major bleeding or clinically relevant non-major bleeding were not adequately reported in the study and were excluded from the current review. Overall, the trial suggested that aspirin offers a clinically relevant and significant benefit in reducing symptomatic VTE (RR 36%, 95% CI 19,50), bleeding risk was not reported and the risk of bias in the trial is assessed to be severe.
Equality	Approximately one third of patients presenting to hospital with a fragility hip fracture have chronic cognitive impairment and another ten percent will be acutely confused. A trial in this population will need to include this very large subgroup of patients. Recent trials (ISRCTN39085558 & 92825709 & 18393176) in hip fracture UK have successfully recruited samples that include patients with and without cognitive impairment.

Study design	RCT or large cluster randomised trial with an economic evaluation.
Feasibility	The population of hip fractures in England are collected annually in a national audit. The annual incidence of hip fracture in England is 70,000, treated in 177 hospitals each of which already contribute to the audit. Outcomes can be derived from linkage to currently available routinely-collected datasets. There is already a large cohort study collecting patient-level health-related quality of life in patients with hip fracture.[217] Clinical equipoise is clearly apparent with some units making local recommendations that differ from the NICE VTE prophylaxis guidance. Current NICE recommendations involve all patients receiving the more costly intervention of LMWH for prophylaxis so that any trial would not require excess treatment costs.
Other comments	It is likely that only NIHR would be able to fund such a trial. This research question is not of interest to pharmaceutical companies as aspirin is not a financially attractive treatment for commercial investment. The committee wished to note that many older people taking aspirin are often co-prescribed proton pump inhibitors (PPIs) to prevent gastrointestinal bleeding.[554,615]
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

R.5 Duration of prophylaxis for elective total hip replacement surgery

Research question: What is the clinical and cost effectiveness of standard versus extended duration pharmacological prophylaxis for preventing VTE in people undergoing elective total hip replacement surgery?

Why this is important:

In 2015, there were 84,462 hip replacements in England, Wales and Northern Ireland. The current recommended duration of prophylaxis is 28 days in the elective total hip replacement population. This extended duration of prophylaxis is based on few, small, and older trials. The quality of the evidence supporting extended duration prophylaxis is very low. Modern pharmaceutical trials of newer interventions use extended duration prophylaxis based on these historical data, with the added incentive of more expensive prophylaxis strategies. There is a large potential cost saving if a shorter duration of prophylaxis is as clinically effective, given the considerable cost of prophylaxis and the number of people for whom it is prescribed.

Criteria for selecting high-priority research recommendations

PICO question	Population:
	• Patients undergoing elective hip replacement
	Intervention(s):
	• LMWH alone for 7 days post-operatively
	Comparison:
	• LMWH alone for 28 days post-operatively
	Outcome(s):
	• Measures of effectiveness
	  ○ All cause and cause-specific mortality (assessed at 90 days post-operatively)
	  ○ Pulmonary embolism (assessed at 90 days post-operatively)
	  ○ DVT (assessed at 90 days post-operatively)

	○ Quality of life (EQ-5D) (assessed at one year post-operatively) • Measures of harm: ○ Major bleeding (assessed at 28 days post-operatively) ○ Clinically relevant non-major bleeding (to include surgical site bleeding) assessed at 28 days post-operatively ○ All cause unplanned return to theatre • Resource use ○ Length of stay ○ Readmission
Importance to patients or the population	LMWH is the primary prophylactic agent of choice in the UK for patients undergoing elective hip replacement, prescribed for over 71,000 patients in 2015 (National Joint Registry, thromboprophylaxis regime for primary hip replacement patients, prescribed at the time of operation, 2015. Currently, LMWH for prophylaxis is recommended for 28 days. This drug is administered via subcutaneous injection performed by the patient themselves or a nurse attending the patient's residence. Patient adherence and satisfaction may be substantially improved with a shorter course of treatment that is as effective. In addition the inherent bleeding risk of prophylaxis is related to the duration of treatment so that shorter durations of prophylaxis may cause less harm to patients.
Relevance to NICE guidance	Current VTE prophylaxis guidance recommends extended duration treatments only. These prophylaxis strategies have been developed based upon historical trials supporting extended duration prophylaxis. Up to date evidence which could support or refute extended prophylaxis would substantially change the recommendation.
Relevance to the NHS	In 2015, there were 84,462 hip replacements in England, Wales and Northern Ireland (NJR report 2016). A shorter and cheaper but clinically effective prophylaxis strategy could potentially generate considerable cost savings for the NHS given the number of hip replacements performed annually. VTE prophylaxis continues to be a controversial clinical question with many trauma and orthopaedic surgeons believing that shorter treatments areas effective. Addressing this research question could help resolve this issue.
National priorities	The National VTE Prevention Programme in England that was initiated in 2010 to reduce the incidence of VTE within a policy framework for VTE risk assessment together with guidance on appropriate prophylaxis. The NHS Outcomes Framework 2016-2017 [249] has highlighted 'deaths from VTE related events' as an area for improvement in reducing the incident of avoidable harm.
Current evidence base	Extended duration prophylaxis strategies have become the standard of care following three small trials, together only reporting data from between 179 and 895 participants for various outcomes. This paucity of evidence, and the very low control event risks, in the order of 1 per 1000, means that the imprecision around the effect estimates is very considerable. Coupled with this the quality of the evidence was assessed to be low or very low, due to risk of bias as well as imprecision. Overall, the committee lacked confidence in the quality of the evidence.
Equality	No known inequalities.
Study design	RCT or large cluster randomised trial with an economic evaluation.
Feasibility	The population of patients undergoing elective hip replacement in England are collected annually in a national audit. The annual incidence of hip replacement in England, Wales and NI is approximately 85,000, treated in approximately 400 hospitals each of which already contribute to the audit. Outcomes can be derived from linkage to currently available routinely-collected datasets, including the national PROMS initiative housed with NHS Digital which collects both functional outcome and health-related quality of life scores.

	Clinical equipoise is clearly apparent with some units making local recommendations that differ from the NICE VTE prophylaxis guidance. Current NICE recommendations involve all patients receiving the more costly intervention of extended duration prophylaxis so that any trial would not require excess treatment costs.
Other comments	It is likely that only NIHR would be able to fund such a trial. This research question is not of interest to pharmaceutical companies as shortened durations of prophylaxis are not a financially attractive strategy for commercial investment.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

Other research recommendations

- What is the effectiveness of different pharmacological prophylaxis strategies (alone or in combination) for people with central venous catheters?
- What is the clinical and cost effectiveness of fixed dose compared to weight-adjusted dose of LMWH for pregnant women admitted to hospital (including up to 6 weeks after giving birth)?
- What is the burden of VTE associated disease and risk factors (including antipsychotic drugs) in psychiatric inpatients?
- What is the clinical and cost effectiveness of IPCD in combination with pharmacological prophylaxis strategies for people with fragility fractures of the pelvis, hip or proximal femur?
- What is the clinical and cost effectiveness of aspirin alone for VTE prophylaxis in people undergoing elective total hip replacement surgery?

Appendix S: How this guideline was updated

March 2018

This guideline is a partial update of NICE guideline CG92 (published January 2010) and will replace it. All chapters in CG92 have been updated in this guideline, except for the following 3 chapters which have been carried over:

- Mechanical VTE prophylaxis – anti-embolism stockings
- Nursing care: early mobilisation and hydration
- Anaesthesia.

New recommendations have been added on the risk assessment and prevention of VTE.

Recommendations are marked as **[2018]** if the recommendation is new or the evidence has been reviewed.

NICE proposes to delete some recommendations from the 2010 guideline, because either the evidence has been reviewed and the recommendations have been updated, or NICE has updated other relevant guidance and has replaced the original recommendations. Recommendations that have been deleted or changed sets out these recommendations and includes details of replacement recommendations. Where there is no replacement recommendation, an explanation for the proposed deletion is given. Recommendations not listed in this section that were in the 2010 guideline have been part of an evidence review and are listed in the main list of recommendations. These are labelled as [2018].

Where recommendations are shaded in grey and end **[2010]**, the evidence has not been reviewed since the original guideline.

Where recommendations are shaded in grey and end **[2010, amended 2018]**, the evidence has not been reviewed but changes have been made to the recommendation wording that change the meaning (for example, because of equalities duties or a change in the availability of medicines, or incorporated guidance has been updated). These changes are marked with yellow shading, and explanations of the reasons for the changes are given in 'Recommendations that have been deleted or changed' for information.

Recommendations that have been deleted or changed

Table 322: Recommendations to be deleted

Recommendation in 2010 guideline	Comment
Base the choice of mechanical VTE prophylaxis on individual patient factors including clinical condition, surgical procedure and patient preference. Choose any one of: • anti-embolism stockings (thigh or knee length) • foot impulse devices • intermittent pneumatic compression devices (thigh or knee length). For patients who are admitted for stroke see recommendations 1.4.2, 1.4.4 and 1.4.5. (1.3.1)	This recommendation has been deleted because the type of mechanical prophylaxis has been specified in each population recommendation.

Recommendation in 2010 guideline	Comment
Show patients how to use anti-embolism stockings correctly and ensure they understand that this will reduce their risk of developing VTE. (1.3.10)	This recommendation has been deleted because it is a duplication of information in recommendations 1.3.2 and 1.2.2.
Base the choice of pharmacological VTE agents on local policies and individual patient factors, including clinical condition (such as severe renal impairment or established renal failure) and patient preferences. (1.3.14)	This recommendation has been deleted as it is now covered in population specific recommendations, a generic recommendation about balance risk, and a renal impairment recommendation.
Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment. (1.5.2)	This recommendation has been deleted because the committee noted that now an advanced decision can be made about whether to stop antiplatelet therapy. It does not need to be made 1 week before surgery.
Consider offering temporary inferior vena caval filters to patients who are at very high risk of VTE (such as patients with a previous VTE event or an active malignancy) and for whom mechanical and pharmacological VTE prophylaxis are contraindicated (1.2.4)	This recommendation has been deleted partly for two reasons: 1. vena caval filters are considered as a method of prophylaxis in individual population reviews. No evidence was identified to support a recommendation for their use. 2. Evidence used in CG92 related to secondary prevention of VTE which is excluded from this update.

Table 323: Amended recommendation wording (change to meaning)

Recommendation in 2012 guideline	Recommendation in current guideline	Reason for change
1.3.2 Do not offer anti-embolism stockings to patients who have: • suspected or proven peripheral arterial disease • peripheral arterial bypass grafting • peripheral neuropathy or other causes of sensory impairment • any local conditions in which stockings may cause damage, for example fragile 'tissue paper' skin, dermatitis, gangrene or recent skin graft • known allergy to material of manufacture • cardiac failure • severe leg oedema or pulmonary oedema from congestive heart failure • unusual leg size or shape • major limb deformity preventing correct fit. Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds. [2010]	1.3.1 Do not offer anti-embolism stockings to people who have: • suspected or proven peripheral arterial disease • peripheral arterial bypass grafting • peripheral neuropathy or other causes of sensory impairment • any local conditions in which anti-embolism stockings may cause damage for example, fragile 'tissue paper' skin, dermatitis, gangrene or recent skin graft • known allergy to material of manufacture • severe leg oedema • major limb deformity or unusual leg size or shape preventing correct fit • stroke (see recommendations 1.3.20-1.3.23). Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds. [2010, amended 2018]	Minor edits to clarify meaning Cross referred to stroke recommendations to highlight stockings are not recommended for stroke patients.
1.3.9 Discontinue the use of anti-embolism stockings if there is	1.3.9 Stop the use of anti-embolism stockings if there is marking,	'Discontinue' changed to 'stop' for plain English

Recommendation in 2012 guideline	Recommendation in current guideline	Reason for change
marking, blistering or discolouration of the skin, particularly over the heels and bony prominences, or if the patient experiences pain or discomfort. If suitable, offer a foot impulse or intermittent pneumatic compression device as an alternative. [2010]	blistering or discolouration of the skin, particularly over the heels and bony prominences, or if the person experiences pain or discomfort. If suitable, offer intermittent pneumatic compression as an alternative. [2010, amended 2018]	purposes, and 'patient' change to 'person'. The words 'Foot impulse' and 'devices' deleted from recommendations because the committee noted that the term intermittent pneumatic compression covers both sleeves applied to the legs and garments wrapped around the foot. The options are considered equal in the recommendations the committee left it to clinicians to decide which were most suitable.
1.3.12 Do not offer foot impulse or intermittent pneumatic compression devices to patients with a known allergy to the material of manufacture. [2010]	1.3.10 Do not offer intermittent pneumatic compression to people with a known allergy to the material of manufacture. [2010, amended 2018]	The words 'Foot impulse' and 'devices' deleted from recommendations because the committee noted that the term intermittent pneumatic compression covers both sleeves applied to the legs and garments wrapped around the foot. The options are considered equal in the recommendations the committee left it to clinicians to decide which were most suitable.
1.3.13 Encourage patients on the ward who have foot impulse or intermittent pneumatic compression devices to use them for as much of the time as is possible and practical, both when in bed and when sitting in a chair. [2010]	1.3.11 Advise the person to wear their device for as much time as possible. [2010, amended 2018]	Edited to simplify wording.

Table 324: Changes to recommendation wording for clarification only (no change to meaning)

Recommendation numbers in current guideline	Comment
1.3.2	Change made from passive to active text.
1.3.2, 1.3.3,1.3.6, 1.3.7, 1.3.12, 1.3.14, 1.3.49	Changes made from 'patients' to 'people'.

Appendix T: NICE technical team

Name	Role
Sarah Willett	Guideline Lead
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Judith Thornton	Technical Lead
Jamie Elvidge	Health Economist
Ian Mather	Resource Impact Lead
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