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Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism.
Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD006771.
DOI: 10.1002/14651858.CD006771.pub3.

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[Intervention Review]

Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism

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Editorial group: Cochrane Vascular Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 11, 2018.

Citation: Robertson L, Strachan J. Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD006771. DOI: 10.1002/14651858.CD006771.pub3.

ABSTRACT

Background

Venous thromboembolism (VTE) is a prevalent and serious condition. Its medical treatment requires anticoagulation, usually with either unfractionated or low molecular weight heparin (LMWH). Administration of unfractionated heparin (UFH) is usually intravenous (IV) but can be subcutaneous as well. This is an update of a review first published in 2009.

Objectives

To assess the effects of subcutaneous UFH versus intravenous UFH, subcutaneous LMWH or any other anticoagulant drug for the initial treatment of venous thromboembolism.

Search methods

For this update, the Cochrane Vascular Information Specialist searched the Specialised Register (last searched 30 November 2016) and CENTRAL (2016, Issue 10). The Cochrane Vascular Information Specialist also searched trials registries for details of ongoing or unpublished studies.

Selection criteria

Randomised controlled trials comparing subcutaneous UFH to control, such as subcutaneous LMWH, continuous intravenous UFH or other anticoagulant drugs in participants with acute venous thromboembolism.

Data collection and analysis

Two review authors (JS and LR) independently extracted data and assessed the risk of bias in the trials. We used meta-analyses when we considered heterogeneity low. The primary outcomes were symptomatic recurrent venous thromboembolism (deep vein thrombosis and/or pulmonary embolism), VTE-related mortality, adverse effects of treatment including major bleeding, and all-cause mortality. We calculated all outcomes using an odds ratio (OR) with a 95% confidence interval (CI).

Main results

We included one additional study in this update, bringing the total number of studies in the review to 16 randomised controlled trials, with a total of 3593 participants (1745 participants in the intervention group and 1848 participants in the control group). Eight trials used intravenous UFH as the control treatment, seven trials used LMWH, and one trial had three arms with both drugs as the controls. We did not identify trials comparing subcutaneous UFH with other anticoagulant drugs. We downgraded the quality of the evidence to low due to lack of blinding in studies, which led to a risk of performance bias, and also for imprecision, as reflected by the wide confidence intervals.

When comparing subcutaneous versus IV UFH, there was no difference in the incidence of symptomatic recurrent VTE at three months (odds ratio (OR) 1.66, 95% confidence interval (CI) 0.89 to 3.10; 8 studies; N = 965; low-quality evidence), symptomatic recurrent deep vein thrombosis (DVT) at three months (OR 3.29, 95% CI 0.64 to 17.06; 1 study; N = 115; low-quality evidence), pulmonary embolism (PE) at three months (OR 1.44, 95% CI 0.73 to 2.84; 9 studies; N = 1161; low-quality evidence), VTE-related mortality at three months (OR 0.98, 95% CI 0.20 to 4.88; 9 studies; N = 1168; low-quality evidence), major bleeding (OR 0.91, 95% CI 0.42 to 1.97; 4 studies; N = 583; low-quality evidence) or all-cause mortality (OR 1.74, 95% CI 0.67 to 4.51; 8 studies; N = 972; low-quality evidence). There were no episodes of asymptomatic VTE occurring within three months of the commencement of treatment.

When comparing subcutaneous UFH versus LMWH, there was no difference in the incidence of recurrent VTE at three months (OR 1.01, 95% CI 0.63 to 1.63; 5 studies; N = 2156; low-quality evidence), recurrent DVT at three months (OR 1.38, 95% CI 0.73 to 2.63; 3 studies; N = 1566; low-quality evidence), PE (OR 0.84, 95% CI 0.36 to 1.96; 5 studies, N = 1819; low-quality evidence), VTE-related mortality (OR 0.53, 95% CI 0.17 to 1.67; 8 studies; N = 2469; low-quality evidence), major bleeding (OR 0.72, 95% CI 0.43 to 1.20; 5 studies; N = 2300; low-quality evidence) or all-cause mortality (OR 0.73, 95% CI 0.50 to 1.07; 7 studies; N = 2272; low-quality evidence). There were no episodes of asymptomatic VTE occurring within three months of the commencement of treatment.

Authors' conclusions

There is no evidence of a difference between subcutaneous versus intravenous UFH for preventing VTE recurrence, VTE-related or all-cause mortality, and major bleeding. According to GRADE criteria, the quality of the evidence was low. There is also no evidence of a difference between subcutaneous UFH and LMWH for preventing VTE recurrence, VTE-related or all-cause mortality or major bleeding.

PLAIN LANGUAGE SUMMARY

Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism

Background

Venous thromboembolism (VTE) is a condition where a blood clot forms in the deep veins (most commonly of the leg) and can travel up to block the arteries in the lungs (a life-threatening condition known as pulmonary embolism). Treating VTE requires injections of a drug called heparin, which stops further clots forming. Heparin comes in two forms: unfractionated heparin (UFH) and low molecular weight heparin (LMWH). UFH can be administered as a continuous intravenous (IV) infusion or intermittently as an injection under the skin (subcutaneous), while LMWH is injected subcutaneously. This review measures the effects of subcutaneous UFH versus IV UFH and LMWH for preventing recurrent clots, mortality and major bleeding. This is an update of a review published in 2009.

Key results

After searching for relevant studies up to November 2016, we found one study to add to this update. In total, we included 16 randomised controlled trials in 3593 participants in this review. This update showed that there was no evidence of a difference between subcutaneous UFH versus intravenous UFH or subcutaneous LMWH for preventing recurrent clots, death or major bleeding.

Quality of the evidence

The quality of the evidence was low due to lack of blinding in the included studies and imprecision of the results due to the small number of reported events.

Summary of findings for the main comparison. Subcutaneous unfractionated heparin compared to intravenous unfractionated heparin for the initial treatment of venous thromboembolism

Subcutaneous unfractionated heparin compared to intravenous unfractionated heparin for the initial treatment of venous thromboembolism

Patient or population: people aged ≥ 18 years with a diagnosis of new or recurrent VTE
Setting: inpatient and outpatient
Intervention: subcutaneous unfractionated heparin
Comparison: intravenous unfractionated heparin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Risk with intravenous unfractionated heparin	Risk with subcutaneous unfractionated heparin			
Symptomatic recurrent VTE at 3 months	Study population		OR 1.66 (0.89 to 3.10)	965 (8 RCTs)	⊕⊕⊖⊖ Low[a]
	35 per 1000	57 per 1000 (32 to 102)			
Symptomatic recurrent DVT at 3 months	Study population		OR 3.29 (0.64 to 17.06)	115 (1 RCT)	⊕⊕⊖⊖ Low[b]
	34 per 1000	105 per 1000 (22 to 379)			
PE at 3 months	Study population		OR 1.44 (0.73 to 2.84)	1161 (9 RCTs)	⊕⊕⊖⊖ Low[c]
	26 per 1000	37 per 1000 (19 to 70)			
VTE-related mortality at 3 months	Study population		OR 0.98 (0.20 to 4.88)	1168 (9 RCTs)	⊕⊕⊖⊖ Low[c]
	3 per 1000	3 per 1000 (1 to 17)			
Major bleeding[d] (7 days - 12 months)	Study population		OR 0.91 (0.42 to 1.97)	583 (4 RCTs)	⊕⊕⊖⊖ Low[e]
	48 per 1000	44 per 1000 (21 to 91)			

All-cause mortality (5 days to 12 months)	Study population		OR 1.74 (0.67 to 4.51)	972 (8 RCTs)	⊕⊕⊖⊖ Low[a]
	12 per 1000	21 per 1000 (8 to 54)			
Asymptomatic VTE at 3 months	No study measured this outcome				

*The basis for the **assumed risk** was the average risk in the intravenous unfractionated heparin group (i.e. the number of participants with events divided by total number of participants of the intravenous heparin group included in the meta-analysis). **The risk in the subcutaneous unfractionated heparin group** (and its 95% confidence interval) is based on the assumed risk in the intravenous unfractionated heparin group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **DVT**: deep vein thrombosis; **PE**: pulmonary embolism; **RCT**: randomised controlled trial; **OR**: odds ratio; **VTE**: venous thromboembolism

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded the quality of the evidence to low due to a high risk of performance bias in eight studies (Andersson 1982; Belcaro 1999; Bentley 1980; Doyle 1987; Krähenbühl 1979; Lopaciuk 1990; Pini 1990; Walker 1987), plus a high risk of attrition bias in five studies (Andersson 1982; Belcaro 1999; Bentley 1980; Krähenbühl 1979; Pini 1990). We also downgraded for imprecision, as reflected by the wide confidence intervals.
[b]We downgraded the quality of the evidence to low for imprecision as only one study with a small number of participants was included, leading to a wide confidence interval around the effect estimate (Hull 1986).
[c]We downgraded the quality of the evidence to low due to a high risk of performance bias in seven studies (Andersson 1982; Bentley 1980; Doyle 1987; Krähenbühl 1979; Lopaciuk 1990; Pini 1990; Walker 1987), plus a high risk of attrition bias in four studies (Andersson 1982; Bentley 1980; Krähenbühl 1979; Pini 1990). We also downgraded for imprecision reflected by the wide confidence intervals.
[d] Major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) (Schulman 2005); fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; any combination of the above.
[e]We downgraded the quality of the evidence to low due to a high risk of performance bias in three studies (Doyle 1987; Lopaciuk 1990; Pini 1990), plus a high risk of attrition bias in one study (Pini 1990). We also downgraded for imprecision, as reflected by the wide confidence intervals.

Summary of findings 2. Subcutaneous unfractionated heparin compared to low molecular weight heparin for the initial treatment of venous thromboembolism

Subcutaneous unfractionated heparin compared to low molecular weight heparin for the initial treatment of venous thromboembolism

Patient or population: people aged ≥ 18 years with a diagnosis of new or recurrent VTE
Setting: inpatient and outpatient
Intervention: subcutaneous unfractionated heparin
Comparison: low molecular weight heparin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Risk with low molecular weight heparin	Risk with subcutaneous unfractionated heparin			
Symptomatic recurrent VTE at 3 months	Study population		OR 1.01 (0.63 to 1.63)	2156 (5 RCTs)	⊕⊕⊖⊖ Low[a]
	31 per 1000	32 per 1000 (20 to 50)			
Symptomatic recurrent DVT at 3 months	Study population		OR 1.38 (0.73 to 2.63)	1566 (3 RCTs)	⊕⊕⊖⊖ Low[b]
	20 per 1000	28 per 1000 (15 to 52)			
PE at 3 months	Study population		OR 0.84 (0.36 to 1.96)	1819 (5 RCTs)	⊕⊕⊖⊖ Low[a]
	12 per 1000	10 per 1000 (4 to 23)			
VTE-related mortality at 3 months	Study population		OR 0.53 (0.17 to 1.67)	2469 (8 RCTs)	⊕⊕⊖⊖ Low[c]
	6 per 1000	3 per 1000 (1 to 11)			
Major bleeding[d] (3 months)	Study population		OR 0.72 (0.43 to 1.20)	2300 (5 RCTs)	⊕⊕⊖⊖ Low[a]
	31 per 1000	23 per 1000 (14 to 37)			
All-cause mortality (7 days - 3 months)	Study population		OR 0.73 (0.50 to 1.07)	2272 (7 RCTs)	⊕⊕⊖⊖ Low[e]
	58 per 1000	43 per 1000 (30 to 62)			
Asymptomatic VTE at 3 months	No study measured this outcome				

*The basis for the **assumed risk** was the average risk in the low molecular weight heparin group (i.e. the number of participants with events divided by total number of participants of the low molecular weight heparin group included in the meta-analysis). **The risk in the subcutaneous unfractionated heparin group** (and its 95% confidence interval) is based on the assumed risk in the low molecular weight heparin group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **DVT**: deep vein thrombosis; **PE**: pulmonary embolism; **RCT**: randomised controlled trial; **OR**: odds ratio; **VTE**: venous thromboembolism

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]We downgraded the quality of the evidence to low due to high risk of selection and reporting bias in one study (Holm 1986), plus a high risk of performance bias in four studies (Kearon 2006; Leizorovicz 2011; Lopaciuk 1992; Prandoni 2004). We also downgraded for imprecision, as reflected by the wide confidence intervals.
[b]We downgraded the quality of the evidence to low due to a high risk of performance bias in three studies (Kearon 2006; Lopaciuk 1992; Prandoni 2004). We also downgraded for imprecision, as reflected by the wide confidence intervals.
[c]We downgraded the quality of the evidence to low due to a high risk of performance bias in seven studies (Belcaro 1999; Faivre 1987; Kearon 2006; Leizorovicz 2011; Lopaciuk 1992; Peternel 2002; Prandoni 2004), a high risk of attrition bias in three studies (Belcaro 1999; Faivre 1987; Peternel 2002), and a high risk of selection and reporting bias in one study (Holm 1986). We also downgraded for imprecision, as reflected by the wide confidence intervals.
[d] Major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) (Schulman 2005); fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; any combination of the above.
[e]We downgraded the quality of the evidence to low due to a high risk of performance bias in six studies (Faivre 1987; Kearon 2006; Leizorovicz 2011; Lopaciuk 1992; Peternel 2002; Prandoni 2004), a high risk of attrition bias in two studies (Faivre 1987; Peternel 2002), and a high risk of selection and reporting bias in one study (Holm 1986). We also downgraded for imprecision reflected by the wide confidence intervals.

BACKGROUND

Description of the condition

Venous thromboembolism (VTE) describes the formation of thrombus in the deep veins, most commonly in the legs (deep vein thrombosis, or DVT). VTE may also refer to the subsequent embolisation of all or part of the thrombus to the pulmonary circulation (pulmonary embolism, or PE). DVT of the lower limbs may be associated with localised pain, swelling and erythema as well as the development of pulmonary emboli and the later occurrence of post-thrombotic syndrome (persistent swelling, erythema and ulceration). PE presents acutely with shortness of breath, pain on inspiration, tachycardia and right heart overload, and if untreated, it can lead to chronic thromboembolic pulmonary hypertension, acute circulatory collapse and death. Increasingly, in the era of more liberal central venous catheterisation, DVT may involve the upper extremities. Rarely, it may also affect other venous circulation (cerebral veins, portal and mesenteric veins, etc.).

In addition to DVT and PE, thrombus can also form in the superficial veins, where it is associated with local pain and inflammation (superficial venous thrombosis). This tends to be associated with lower mortality and morbidity rates than DVT, although some patients may be at a higher risk of DVT formation depending on the location of the clot (Chengelis 1996; Nasr 2015).

Venous thromboembolism (VTE) is comprised of DVT and PE and can occur spontaneously. However, there are many risk factors for VTE, including periods of inactivity, dehydration, hospitalisation, trauma, clotting disorders and previous thrombosis, varicose veins with phlebitis, pregnancy, oral combined hormonal contraceptives, malignancy, obesity, smoking, and age (Anderson 2003; NICE 2010).

The incidence of VTE in mostly white populations is between 100 and 200 per 100,000 person-years (Heit 2015; White 2003). Of these, it is estimated that 45 to 117 cases per 100,000 person-years are due to DVT (without PE), and 29 to 78 are due to PE (with or without DVT) (Heit 2015). Recurrent VTE occurs in approximately 7.4% of patients at 1 year and up to 30.4% of patients by 10 years (Cushman 2007; Heit 2015; White 2003).

Description of the intervention

Heparin is a heterogeneous mixture of branched glycosaminoglycans (GAG), discovered in 1916 (McLean 1916).

The anticoagulant action of heparin requires the binding of antithrombin (AT). Heparin binds to AT through a unique glucosamine unit that is contained within a pentasaccharide sequence present in a fraction of the GAG molecules. Currently, three therapeutic heparin preparations are available for clinical use: unfractionated heparin (UFH) with a molecular weight of approximately 15,000 daltons; its derivative low molecular weight heparin (LMWH), with an average molecular weight of 4000 to 5000 daltons; and the significantly more expensive pentasaccharide. Although LMWH has largely replaced UFH in the setting of acute VTE treatment, many people do not benefit from its use due to increased risk of complications, specifically bleeding in patients with severe renal failure.

How the intervention might work

Complications of heparin use may include bleeding; heparin-induced thrombocytopenia (HIT); and in the long term, heparin-induced osteoporosis. Consequently, it is important to monitor coagulation factors, specifically the activated partial thromboplastin time (aPTT), when using UFH. There are two preferred modes of administering this treatment: a continuous intravenous (IV) mode and an intermittent subcutaneous mode. Depending on the method chosen, pharmacokinetic analyses demonstrate differences in heparin bioavailability and early achievement of a therapeutic aPTT goal, favouring the intravenous route (Hull 1986).

Nevertheless, investigators have evaluated the subcutaneous route of administration for VTE due to its ease of application, early mobilisation and hospital discharge, and presumably less line-related complications. People have received the treatment either in weight-adjusted or aPTT-adjusted doses, and investigators have compared results with other available treatment modalities.

Why it is important to do this review

Two meta-analyses comparing LMWH versus intravenous UFH have shown LMWH to be non-inferior to UFH with regards to recurrent DVT, PE, bleeding and thrombocytopenia (reduction in the number of platelets) (Dolovich 2000; Quinlan 2004). However, there were no trials utilising subcutaneous UFH for this indication in these analyses. The present review was originally completed in 2009 (Vardi 2009), and an update is necessary to incorporate evidence from any new studies completed since then. Additionally, Cochrane has developed new methodology during that time that should be incorporated in the updated review.

OBJECTIVES

To assess the effects of subcutaneous UFH versus intravenous UFH, subcutaneous LMWH or any other anticoagulant drug for the initial treatment of venous thromboembolism.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing the effects of subcutaneous UFH versus intravenous UFH, LMWH or any other anticoagulant drug for the initial treatment of venous thromboembolism. We included trials with more than two treatment groups and analysed them accordingly. We did not expect to find any cross-over trials in the setting of VTE. We included trials with interventions and follow-up periods of any duration.

We excluded randomised controlled trials without truly random allocation to the treatment or control group or without allocation concealment, in view of the fact that prior knowledge of treatment allocation may have led to biased participant allocation, treatment or reporting. After allocation, further concealment of treatment may be impossible due to the differences between preparations and routes of administration. Thus, despite recognising that this may lead to biased treatment or reporting, post-allocation blinding was not a prerequisite, and we addressed it in a sensitivity analysis.

We acknowledge that non-randomised studies or studies using other randomisation methods (for example cluster randomisation) may provide useful information about this problem. However, for this review, we did not consider such studies.

Types of participants

Adults (aged 18 years or older) with a diagnosis of new or recurrent VTE. Ideally, the diagnosis of DVT of the leg was made with the use of compression ultrasonography, colour-coded duplex ultrasonography or contrast venography, and the diagnosis of PE with high probability ventilation-perfusion scan or pulmonary arterial filling defects on computed tomography or invasive angiography.

Types of interventions

Initial treatment with subcutaneous UFH for individuals with VTE, administered at any regimen, in trials of any duration.

1. Subcutaneous UFH:
   a. fixed weight-adjusted dose;
   b. aPTT-adjusted dose.
2. Other treatment modalities:
   a. intravenous UFH;
   b. subcutaneous LMWH;
   c. other.

We expected studies to administer supplementary treatment of VTE with an oral anticoagulant titration. We considered its use in a subgroup analysis.

Types of outcome measures

Primary outcomes

- Incidence of symptomatic recurrent VTE at three months
- Incidence of symptomatic recurrent DVT at three months
- PE at three months
- VTE-related mortality at three months
- Major bleeding (as defined by the International Society on Thrombosis and Haemostasis (ISTH) (Schulman 2005): fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; any combination of the above)
- All-cause mortality

Secondary outcomes

- Incidence of asymptomatic VTE at three months
- Treatment-related morbidity: minor bleeding (bleeding that is clinically overt but not meeting the definition of serious bleeding provided by the ISTH) and heparin-induced thrombocytopenia
- Length of hospital stay
- Quality of life

Search methods for identification of studies

We did not restrict the search for eligible studies by language.

Electronic searches

For this update, the Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials.

- Cochrane Vascular Specialised Register (30 November 2016).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10) via the Cochrane Register of Studies Online.

See Appendix 1 for details of the search strategy used for CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, Embase Ovid, CINAHL, AMED, and through handsearches of relevant journals. The full list of the databases, journals and conference proceedings included in these searches, as well as the search strategies used, are described in the Specialised Register section of the Cochrane Vascular module in the Cochrane Library (www.cochranelibrary.com).

The CIS searched the following trial registries for details of ongoing and unpublished studies.

- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch).
- ISRCTN Register (www.isrctn.com/).

See Appendix 2 for details of the search strategies.

Searching other resources

We handsearched the reference lists of relevant trials and reviews identified for additional studies.

Data collection and analysis

Selection of studies

For this update, two review authors (JS, LR) independently scanned the titles, abstracts and keywords of every record retrieved. We retrieved full articles for further assessment if the information given suggested that the study fulfilled the inclusion criteria and did not meet the exclusion criteria. If there was any doubt regarding these criteria based on the title and abstract, we retrieved the full article for clarification.

Data extraction and management

For studies that fulfilled the inclusion criteria, we abstracted relevant population and intervention characteristics using standard data extraction templates. For details, see Characteristics of included studies and Appendix 3 (Additional study information). We resolved disagreements by discussion.

For this update, two review authors (JS, LR) extracted the following data.

1. **General information**: author, title, publication (published/unpublished; duplicate/multiple publication), language of publication, year of publication, country, complete reference or source, contact details, rural or urban setting, single centre versus multicentre, setting, stated aim of the study, sponsor, ethics committee approval and description of conflict of interests.

2. **Trial design**: prospective study, control group, parallel study, placebo controlled, active-medication controlled, use of cross-over design (and if so, description of run-in period, wash-out period and carry-over effect described), description of period effect, sampling method and power calculation, selection bias (randomisation, unit of randomisation and allocation concealment adequacy), performance bias (blinding of participants and caregivers, method of blinding, check of blinding, check of blinding method), attrition bias (intention-to-treat analysis, description of withdrawals, drop-outs description and losses to follow-up, change of groups (if cross-overs), number of dropouts and withdrawals and loss to follow-up, reasons and description for dropouts, withdrawals or losses to follow-up), and detection bias (blinding of outcome assessors), overall quality assessment, definition of inclusion criteria, definition of exclusion criteria,, and specified subgroups (predefined and defined post hoc).
3. **Participants**: venous thromboembolism (VTE) diagnostic criteria description, VTE diagnostic criteria validity,, baseline characteristics (i.e. number of participants, age, sex, race, body mass index, comorbidities, concomitant medications, identical treatment of groups (apart from intervention)).
4. **Intervention**: dose adjustment for subcutaneous UFH (weight-adjusted or aPTT-adjusted), bolus intravenous heparin in subcutaneous arm, number of daily subcutaneous doses, daily heparin cumulative dose, duration of heparin therapy (days), warfarin dose, length of follow-up, compliance.
5. **Outcomes assessed for short, intermediate and long term as defined above**: incidence of symptomatic recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE), mortality related to propagation of VTE, treatment-related mortality during heparin treatment, incidence of asymptomatic propagation of VTE, treatment-related morbidity during heparin treatment (major bleeding, minor bleeding, heparin-induced thrombocytopenia (HIT), other), length of hospital stay, quality of life.
6. **Effect modifiers**: compliance, change of concomitant medication, warfarin therapy.

We sought any relevant missing information on the trials from the original author(s) of the article, if required.

Assessment of risk of bias in included studies

Two review authors (JS, LR) independently used the Cochrane 'Risk of bias' tool to assess the risk of bias for each of the included studies (Higgins 2011). The tool provides a protocol for judgements on sequence generation, allocation methods, blinding of participants, investigators and outcome assessors, incomplete outcome data, selective outcome reporting and any other relevant biases. We judged each of these domains as being at either high, low or unclear risk of bias according to Higgins 2011 and provided support for each judgement, resolving any disagreements by discussion. We present the conclusions in a 'Risk of bias' table.

Measures of treatment effect

We based the analysis on intention-to-treat data from the individual clinical trials. For the primary and secondary outcomes, which are binary measures, we computed odds ratios (ORs) using a fixed-effect model and calculated the 95% confidence intervals (CI) of the effect sizes. For the continuous outcomes such as length of hospital stay and quality of life, we planned to use mean differences (MDs) with 95% CIs where the scales were the same, and where scales were different but the outcome was the same, we planned to use the standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

We sought relevant missing data from authors where necessary and feasible. We carefully evaluated important numerical data such as screened, eligible and randomised participants as well as intention-to-treat and per-protocol population. We investigated dropouts, losses to follow-up and withdrawn study participants.

Assessment of heterogeneity

We assessed heterogeneity between the trials by visual examination of the forest plot to check for overlapping CIs, the Chi^2 test for homogeneity with a 10% level of significance and the I^2 statistic to measure the degree of inconsistency between the studies. An I^2 result of greater than 50% may represent moderate to substantial heterogeneity (Deeks 2011).

Assessment of reporting biases

We planned to assess publication bias by funnel plots if a sufficient number of studies (10 or more) were available in the meta-analyses. There are many reasons for funnel plot asymmetry, and we planned to consult the *Cochrane Handbook for Systematic Reviews of Interventions* to aid the interpretation of the results (Sterne 2011).

Data synthesis

The review authors independently extracted the data. One review author (LR) entered the data into Review Manager 5 (RevMan 2014), and the second review author (JS) cross-checked data entry. We resolved any discrepancies by consulting the source publication.

If data were available, sufficiently similar and of sufficient quality, we provided a statistical summary. We used a fixed-effect model to meta-analyse the data. If the I^2 statistic indicated heterogeneity greater than 50%, we performed a random-effects model analysis instead.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses, according to the following clinically logical pre-defined groups.

1. Participants.
   a. VTE at randomisation: DVT with/without PE versus DVT without PE versus PE without DVT.
   b. VTE: first versus recurrent.
   c. Severity: haemodynamically stable versus unstable, respiratory stable versus unstable.
   d. Age.
   e. Renal function.
   f. Underlying pathology (e.g. orthopaedic patients).
2. Intervention.
   a. Number of daily subcutaneous heparin injections.
   b. Type of dose adjustment; weight-adjusted versus aPTT-adjusted.

c. Initial intravenous bolus heparin given versus not given.
d. Concomitant oral anticoagulant use.
e. Timing of oral anticoagulant initiation.

We performed neither a dose-response analysis nor any indirect comparisons between groups not directly evaluated head-to-head in a clinical trial.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size, repeating the analysis by:

- excluding data from unpublished studies;
- taking account of study quality, as specified above;
- excluding any very long or large studies to establish how much they dominated the results;
- excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

Summary of findings table

We presented the main findings of the review results in a 'Summary of findings' table, reporting the quality of evidence (according to Atkins 2004), the magnitude of effect of the interventions examined, and the sum of available data on symptomatic recurrent VTE at three months, symptomatic recurrent DVT at three months, PE at three months, VTE-related mortality at three months, major bleeding, all-cause mortality and asymptomatic VTE at three months, . We used the GRADEpro software to assist in the preparation of the 'Summary of findings' table (GRADEpro GDT).

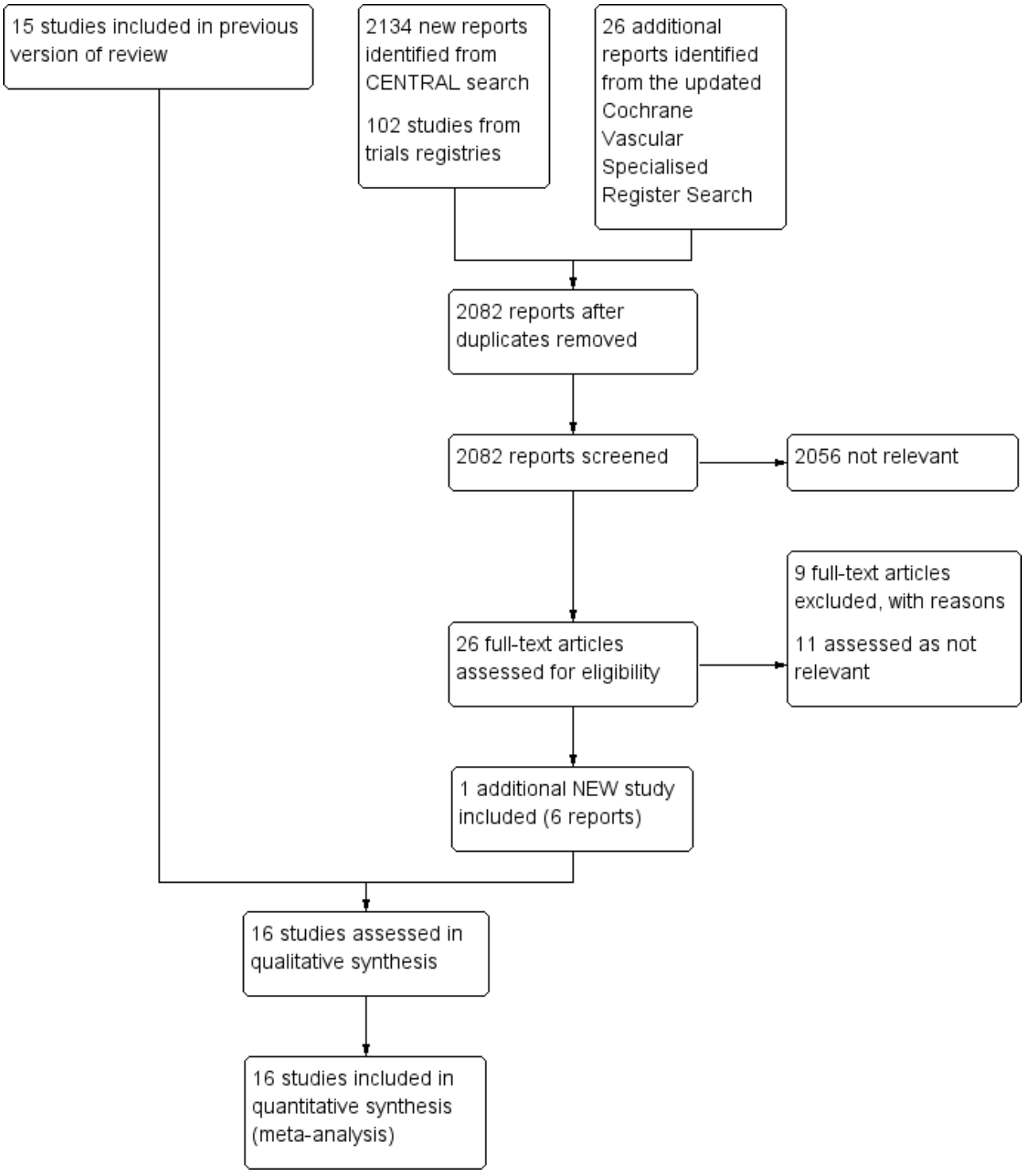
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Included studies

For this update, we identified one additional study that met the inclusion criteria for this review (Leizorovicz 2011), bringing the total number of included studies to 16 randomised controlled trials, involving 3593 participants (Andersson 1982; Belcaro 1999; Bentley 1980; Doyle 1987; Faivre 1987; Holm 1986; Hull 1986; Kearon 2006; Krähenbühl 1979; Leizorovicz 2011; Lopaciuk 1990; Lopaciuk 1992; Peternel 2002; Pini 1990; Prandoni 2004; Walker 1987). For detailed descriptions see Characteristics of included studies and Appendix 3.

Eight studies compared subcutaneous UFH versus intravenous UFH (Andersson 1982; Bentley 1980; Doyle 1987; Hull 1986; Krähenbühl 1979; Lopaciuk 1990; Pini 1990; Walker 1987), seven studies compared subcutaneous UFH versus LMWH (Faivre 1987; Holm

1986; Kearon 2006; Leizorovicz 2011; Lopaciuk 1992; Peternel 2002; Prandoni 2004), and one study compared subcutaneous UFH to both intravenous UFH and subcutaneous LMWH (Belcaro 1999).. For the long-term treatment, nine studies utilised warfarin, three used acenocoumarol, and one used subcutaneous UFH. In three studies, the long-term management was not clear. Thirteen trials monitored the subcutaneous heparin dose through aPTT measurements and one through anti-factor Xa (anti-Xa) measurements, while in two studies the subcutaneous heparin dose was fixed or based solely on weight.

Fourteen studies took place in an inpatient setting (Andersson 1982; Bentley 1980; Doyle 1987; Faivre 1987; Holm 1986; Hull 1986; Krähenbühl 1979; Leizorovicz 2011; Lopaciuk 1990; Lopaciuk 1992; Peternel 2002; Pini 1990; Prandoni 2004; Walker 1987), and two in both inpatient and outpatient settings (Belcaro 1999; Kearon 2006). All trials included participants with DVT. Four trials allowed for participants with PE in their inclusion criteria (Faivre 1987; Kearon 2006; Leizorovicz 2011; Prandoni 2004). Four trials excluded people with PE (Doyle 1987; Holm 1986; Peternel 2002; Walker 1987), and an additional two trials excluded people with massive PE (Faivre 1987; Lopaciuk 1990). The remaining trials did not clearly describe PE inclusion. We did not identify any trials that included only participants with PE. Studies recruited participants upon diagnosis of VTE and randomised them to treatment groups. Eight of the included studies administered an initial intravenous heparin bolus prior to initiating subcutaneous heparin treatment (Andersson 1982; Hull 1986; Krähenbühl 1979; Leizorovicz 2011; Lopaciuk 1990; Lopaciuk 1992; Peternel 2002; Prandoni 2004). One study maintained the infusion for 24 hours before the first subcutaneous administration (Holm 1986). The duration of the intervention ranged from a minimum of seven days to achievement of international normalised ratio (INR) target level for oral anticoagulation in all included trials apart from one, which administered subcutaneous heparin for three months (Belcaro 1999). Diagnostic modalities for DVT included venous occlusion plethysmography, thermography, phlebography, venography, and colour-duplex sonography; as well as lung scan or CT-angiography for PE. Follow-up length was as long as the intervention duration in eight studies and three months in seven studies (Belcaro 1999; Doyle 1987; Hull 1986; Kearon 2006; Lopaciuk 1990; Lopaciuk 1992; Prandoni 2004). One study reported death rate at 12 months (Doyle 1987). One study was terminated early, as an interim safety analysis revealed an excess mortality rate in the subcutaneous heparin group (Leizorovicz 2011).

Excluded studies

After careful evaluation of the full publications, we excluded nine additional studies from this update (Nakamura 2010; NCT01956955; Quiros 2001; Riess 2014; Rodgers 1999; Romera 2009; Ucar 2015; Van Doormaal 2009; Van Doormaal 2010), for a total number of 16 excluded studies. The main reasons for exclusion were the method of administration of heparin and involvement of thrombolysis or VTE prophylaxis. For further details see Characteristics of excluded studies.

Risk of bias in included studies

For details on methodological quality of included studies, see Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

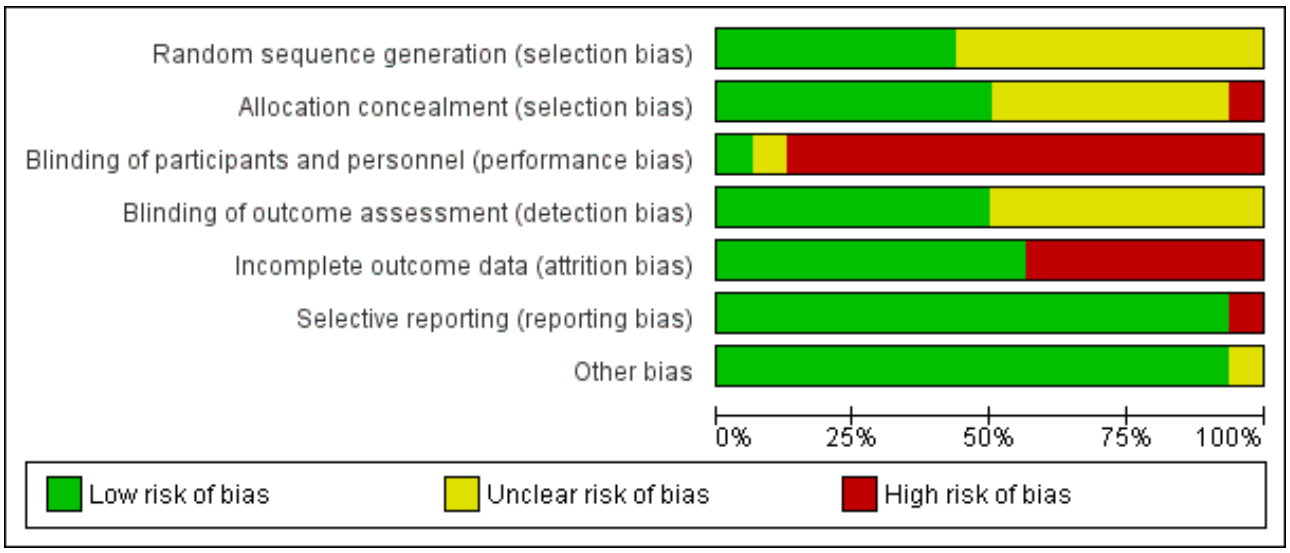
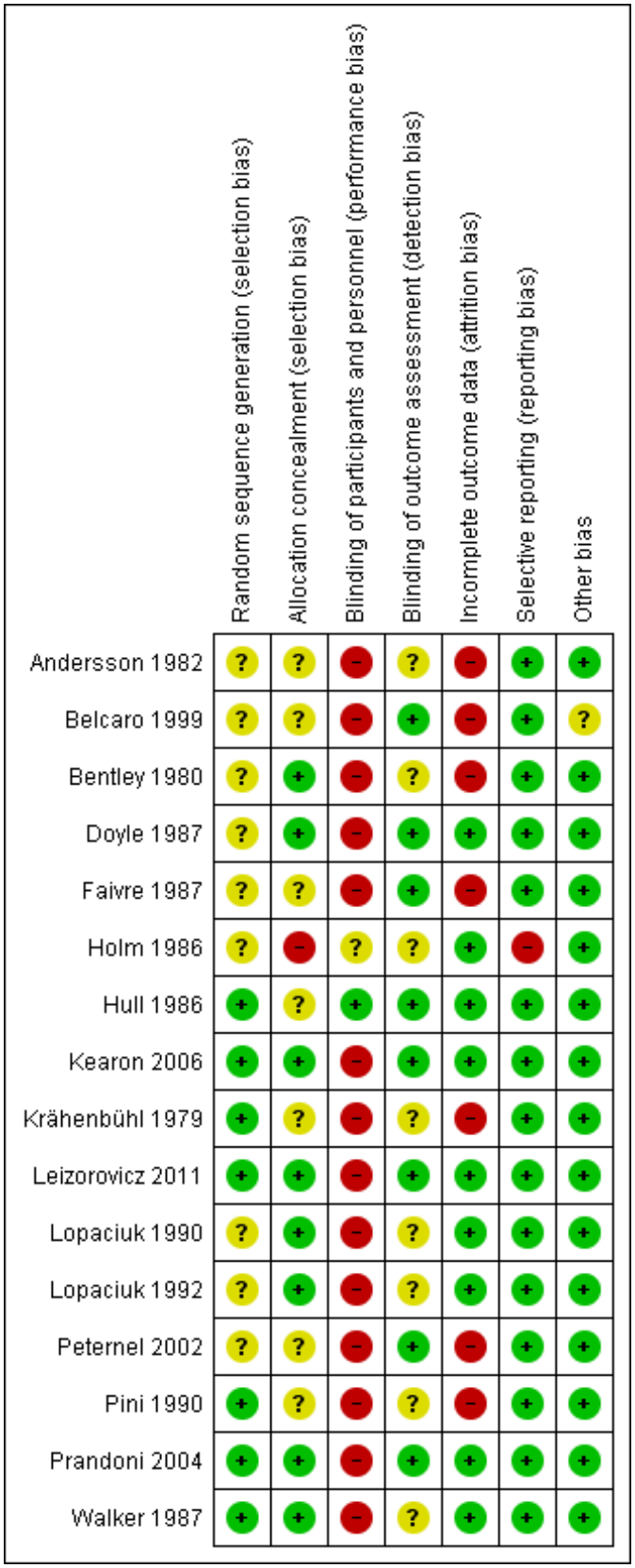


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Five studies described the use of computer-generated random sequences (Hull 1986; Kearon 2006; Leizorovicz 2011; Pini 1990; Prandoni 2004), one study described 'drawing of lots' (Krähenbühl 1979), and another study described the use of a random number table to allocate participants to treatment groups (Walker 1987). We therefore deemed these seven studies to be at low risk of selection bias. All other studies stated that they randomised participants but did not provide a clear description of random sequence generation, so we considered them to be at unclear risk of selection bias (Andersson 1982; Belcaro 1999; Bentley 1980; Doyle 1987; Faivre 1987; Holm 1986; Lopaciuk 1990; Lopaciuk 1992; Peternel 2002).

We judged eight studies to be at low risk of selection bias due to allocation concealment (Bentley 1980; Doyle 1987; Kearon 2006; Leizorovicz 2011; Lopaciuk 1990; Lopaciuk 1992; Prandoni 2004; Walker 1987). Five of these studies described the use of 'sealed envelopes' to maintain allocation concealment (Bentley 1980; Doyle 1987; Lopaciuk 1990; Lopaciuk 1992; Walker 1987). The *Cochrane Handbook for Systematic Reviews of Interventions* states that allocation concealment should be achieved through sequentially numbered, opaque, sealed envelopes, opened only after irreversible assignment to a participant. However, due to the age of the studies included in this review, we decided that studies describing the use of envelopes to maintain allocation concealment would be at lower risk of selection bias than those that did not and that we would deem them to be at low risk. Three studies described the use of central telephone randomisation (Kearon 2006; Leizorovicz 2011; Prandoni 2004). Leizorovicz 2011 specifically stated that "no allocation concealment mechanism was attempted as the study was open"; however, we still considered the study to be at low risk of selection bias, as this statement appeared to contradict the description of "central telephone randomisation". We therefore assumed that the authors were referring to the blinding of participants and personnel as "allocation concealment". Furthermore, authors also stated that "care was taken to ensure that outcome assessors and data analysts were kept blinded to the allocation".

We judged Holm 1986 to be at high risk of selection bias due to allocation concealment. Authors stated that participants' allocations to treatment groups depended on the order of participant admission: "the vials [of low molecular weight or unfractionated heparin] had been randomised in advance and numbered consecutively, the number of patient admission determining the number of vial used". As personnel potentially had knowledge of the order of the vials – allowing them to control the composition of the treatment groups by manipulating the order of participant admission – we deemed this study to be at high risk of selection bias.

No other studies provided descriptions of allocation concealment, so we deemed them to be at unclear risk for allocation concealment (Andersson 1982; Belcaro 1999; Faivre 1987; Hull 1986; Krähenbühl 1979; Peternel 2002; Pini 1990).

Blinding

Only one study adequately reported the blinding of participants and personnel, so we considered it as being at low risk of performance bias (Hull 1986). One study reported that it was "double-blind" but did not provide any further information, so we assessed it as being at unclear risk (Holm 1986). The remaining fourteen studies were not blinded, so we considered them to be at high risk of performance bias (Andersson 1982; Belcaro 1999; Bentley 1980; Doyle 1987; Faivre 1987; Kearon 2006; Krähenbühl 1979; Leizorovicz 2011; Lopaciuk 1990; Lopaciuk 1992; Peternel 2002; Pini 1990; Prandoni 2004; Walker 1987).

For measuring the risk of detection bias, we decided that due to the subjective nature of certain criteria, we would rate studies as being at high risk of detection bias if they did not adequately blind for the following outcomes: recurrent VTE at three months; recurrent DVT at three months; PE – excluding PE found at autopsy; incidence of asymptomatic VTE at three months; quality of life; and incidence of HIT. However, we thought that VTE-related mortality at three months, all-cause mortality and major and minor bleeding (if they followed the definition provided by the International Society on Thrombosis and Haemostasis) were objective enough to not require blinding.

In total, we judged eight studies to be at low risk of detection bias (Belcaro 1999; Doyle 1987; Faivre 1987; Hull 1986; Kearon 2006; Leizorovicz 2011; Peternel 2002; Prandoni 2004). Two studies were only included in the analysis of VTE-related mortality at three months and all-cause mortality, so we automatically deemed them to be at low risk of detection bias (Faivre 1987; Peternel 2002), while six studies adequately blinded for all six subjective outcomes (Belcaro 1999; Doyle 1987; Hull 1986; Kearon 2006; Leizorovicz 2011; Prandoni 2004). The remaining eight studies did not state whether personnel assessing suspected PE were adequately blinded, so we deemed them to be at unclear risk of detection bias (Andersson 1982; Bentley 1980; Holm 1986; Krähenbühl 1979; Lopaciuk 1990; Lopaciuk 1992; Pini 1990; Walker 1987).

Incomplete outcome data

Nine studies adequately accounted for all missing data, and we judged them to be at low risk of attrition bias (Doyle 1987; Holm 1986; Hull 1986; Kearon 2006; Leizorovicz 2011; Lopaciuk 1990; Lopaciuk 1992; Prandoni 2004; Walker 1987). The remaining seven studies did not adequately deal with missing data, so we deemed them to be at high risk of attrition bias (Andersson 1982; Belcaro 1999; Bentley 1980; Faivre 1987; Krähenbühl 1979; Peternel 2002; Pini 1990).

Selective reporting

Due to the age of the studies included in the review, there was only one available protocol for an included study (Kearon 2006). We therefore based our judgements of selective reporting solely on the reporting of pre-specified outcomes in the Methods sections. Fifteen papers reported on all pre-specified outcomes, and we deemed them to be at low risk of reporting bias (Andersson 1982; Belcaro 1999; Bentley 1980; Doyle 1987; Faivre 1987; Hull 1986; Kearon 2006; Krähenbühl 1979; Leizorovicz 2011; Lopaciuk 1990; Lopaciuk 1992; Peternel 2002; Pini 1990; Prandoni 2004; Walker 1987). We considered one study to be at high risk of reporting bias, as authors presented results for leg pain but did not present the method of measuring pain in the Methods section (Holm 1986).

Other potential sources of bias

We rated 15 studies as being at low risk of other bias (Andersson 1982; Bentley 1980; Doyle 1987; Faivre 1987; Holm 1986; Hull 1986; Kearon 2006; Krähenbühl 1979; Leizorovicz 2011; Lopaciuk 1990; Lopaciuk 1992; Peternel 2002; Pini 1990; Prandoni 2004; Walker

1987). We considered the risk of other bias to be unclear in one study, as different groups received treatment in different locations, with groups 1 and 2 receiving different treatments in hospital and group 3 receiving treatment at home (Belcaro 1999).

Effects of interventions

See: **Summary of findings for the main comparison** Subcutaneous unfractionated heparin compared to intravenous unfractionated heparin for the initial treatment of venous thromboembolism; **Summary of findings 2** Subcutaneous unfractionated heparin compared to low molecular weight heparin for the initial treatment of venous thromboembolism

For a summary of outcomes see Summary of findings for the main comparison; Summary of findings 2. For details of outcomes see Data and analyses.

Subcutaneous UFH versus intravenous UFH

Symptomatic recurrent VTE at three months

Eight studies with a combined total of 965 participants measured recurrent VTE at three months (Andersson 1982; Bentley 1980; Doyle 1987; Hull 1986; Krähenbühl 1979; Lopaciuk 1990; Pini 1990; Walker 1987). The rate of recurrence was similar between participants treated with subcutaneous (27 events/485 participants) versus IV UFH (17 events/480 participants), leading to an odds ratio (OR) of 1.66 (95% CI 0.89 to 3.10; N = 965; 8 studies; I^2 = 0%; low-quality evidence; Analysis 1.1). All eight studies excluded participants with PE, so we could not perform subgroup analysis based on VTE at randomisation.

Symptomatic recurrent DVT at three months

One study with 115 participants measured recurrent DVT at three months (Hull 1986), finding a similar rate between participants treated with subcutaneous (6 events/57 participants) versus IV UFH (2 events/58 participants), leading to an OR of 3.29 (95% CI 0.64 to 17.06; N = 115; 1 study; low-quality evidence; Analysis 1.2). This study included only DVT participants, so we could not perform subgroup analysis based on VTE at randomisation.

PE at three months

Nine studies with a combined total of 1161 participants measured incidence of PE at three months (Andersson 1982; Belcaro 1999; Bentley 1980; Doyle 1987; Hull 1986; Krähenbühl 1979; Lopaciuk 1990; Pini 1990; Walker 1987). Incidence was similar between participants treated with subcutaneous (21 events/584 participants) versus IV UFH (15 events/577 participants), leading to an OR of 1.44 (95% CI 0.73 to 2.84; N = 1161; 9 studies; I^2 = 0%; low-quality evidence; Analysis 1.3). All nine studies excluded participants with PE, so we could not perform subgroup analysis based on VTE at randomisation.

VTE-related mortality at three months

Nine studies with a combined total of 1168 participants measured VTE-related mortality at three months (Andersson 1982; Belcaro 1999; Bentley 1980; Doyle 1987; Hull 1986; Krähenbühl 1979; Lopaciuk 1990; Pini 1990; Walker 1987). However, only three studies reported any cases of this outcome (Hull 1986; Lopaciuk 1990; Pini 1990), which was similar for participants treated with subcutaneous (2 events/588 participants) versus IV UFH (2 events/580 participants), leading to an OR of 0.98 (95% CI 0.20 to 4.88; N = 1168; 9 studies; I^2 = 0%; low-quality evidence; Analysis 1.4). All nine studies excluded participants with PE, so we could not perform subgroup analysis based on VTE at randomisation.

Major bleeding

Four studies with a combined total of 583 participants measured incidence of major bleeding during the study period (Doyle 1987; Hull 1986; Lopaciuk 1990; Pini 1990). The incidence of major bleeding was similar between participants treated with subcutaneous (13 events/294 participants) versus IV UFH (14 events/289 participants), leading to an OR of 0.91 (95% CI 0.42 to 1.97; N = 583; 4 studies; I^2 = 0%; low-quality evidence; Analysis 1.5). All four studies excluded participants with PE, so we could not perform subgroup analysis based on VTE at randomisation.

All-cause mortality

Eight studies with a combined total of 972 participants measured all-cause mortality (Andersson 1982; Bentley 1980; Doyle 1987; Hull 1986; Krähenbühl 1979; Lopaciuk 1990; Pini 1990; Walker 1987). This outcome was similar for participants treated with subcutaneous (11 events/489 participants) versus IV UFH (6 events/483 participants), leading to an OR of 1.74 (95% CI 0.67 to 4.51; N = 972; 8 studies; I^2 = 0%; low-quality evidence; Analysis 1.6). All eight studies excluded participants with PE, so we could not perform subgroup analysis based on VTE at randomisation.

Asymptomatic VTE at three months

No studies comparing subcutaneous UFH with IV UFH reported any episodes of asymptomatic VTE occurring within three months of the commencement of treatment.

Treatment-related morbidity

Minor bleeding

Five studies with a combined total of 779 participants measured incidence of minor bleeding during the study period (Belcaro 1999; Doyle 1987; Hull 1986; Lopaciuk 1990; Pini 1990). Incidence was similar for participants treated with subcutaneous (18 events/393 participants) versus IV UFH (26 events/386 participants), leading to an OR of 0.63 (95% CI 0.33 to 1.20; N = 779; 5 studies; I^2 = 0%; low-quality evidence; Analysis 1.7). All five studies excluded participants with PE, so we could not perform subgroup analysis based on VTE at randomisation.

Heparin-induced thrombocytopenia

None of the studies comparing subcutaneous UFH with IV UFH reported episodes of HIT.

Length of hospital stay

The study by Belcaro 1999 measured days in hospital, but the subcutaneous UFH group were treated at home, so we could not make a comparison. The mean (± standard deviation) length of hospital stay in the IV UFH group was 5.4 ± 1.4 days.

Quality of life

None of the included studies measured quality of life as an outcome.

Subcutaneous UFH versus LMWH

Symptomatic recurrent VTE at three months

Five studies with a combined total of 2156 participants measured recurrent VTE at three months (Holm 1986; Kearon 2006; Leizorovicz 2011; Lopaciuk 1992; Prandoni 2004). The rate of recurrent VTE at three months was similar for participants treated with subcutaneous UFH (34 events/1071 participants) versus LMWH (34 events/1085 participants), leading to an OR of 1.01 (95% CI 0.63 to 1.63; N = 2156; 5 studies; I^2 = 0%; low-quality evidence; Analysis 2.1). We observed no differences between the VTE at randomisation subgroups 'DVT with/without PE' versus 'DVT without PE' (P = 0.38).

Symptomatic recurrent DVT at three months

Three studies with a combined total of 1566 participants measured recurrent DVT at three months (Kearon 2006; Lopaciuk 1992; Prandoni 2004), finding similar rates for participants treated with subcutaneous UFH (22 events/780 participants) versus LMWH (16 events/786 participants), leading to an OR of 1.38 (95% CI 0.73 to 2.63; N = 1566; 3 studies; I^2 = 0%; low-quality evidence; Analysis 2.2). We observed no differences between the VTE at randomisation subgroups 'DVT with/without PE' versus 'DVT without PE' (P = 0.37).

PE at three months

Five studies with a combined total of 1819 participants measured incidence of PE at three months (Belcaro 1999; Holm 1986; Kearon 2006; Lopaciuk 1992; Prandoni 2004). Incidence was similar for participants treated with subcutaneous UFH (9 events/906 participants) versus LMWH (11 events/913 participants), leading to an OR of 0.84 (95% CI 0.36 to 1.96; N = 1819; 5 studies; I^2 = 0%; low-quality evidence) (Analysis 2.3). We observed no differences between the VTE at randomisation subgroups 'DVTwith/without PE' versus 'DVT without PE' (P = 0.81).

VTE-related mortality at three months

Eight studies with a combined total of 2469 participants measured VTE-related mortality at three months (Belcaro 1999; Faivre 1987; Holm 1986; Kearon 2006; Leizorovicz 2011; Lopaciuk 1992; Peternel 2002; Prandoni 2004). The outcome was similar for participants treated with subcutaneous UFH (4 events/1230 participants) versus LMWH (8 events/1239 participants), leading to an OR of 0.53 (95% CI 0.17 to 1.67; N = 2469; 8 studies; I^2 = 0%; low-quality evidence; Analysis 2.4). There were no cases of VTE-related mortality in the four studies incorporating participants with DVT but without PE.

Major bleeding

Five studies with a combined total of 2300 participants measured incidence of major bleeding during the study period (Belcaro 1999; Kearon 2006; Leizorovicz 2011; Lopaciuk 1992; Prandoni 2004). The incidence of major bleeding was similar for participants treated with subcutaneous UFH (26 events/1147 participants) versus LMWH (36 events/1153 participants), leading to an OR of 0.72 (95% CI 0.43 to 1.20; N = 2300; 5 studies; I^2 = 0%; low-quality evidence; Analysis 2.5). We observed no differences between the VTE at randomisation subgroups DVT regardless of PE status versus DVT without PE(P = 0.36).

All-cause mortality

Seven studies with a combined total of 2272 participants measured all-cause mortality (Faivre 1987; Holm 1986; Kearon 2006; Leizorovicz 2011; Lopaciuk 1992; Peternel 2002; Prandoni 2004). This outcome was similar for participants treated with subcutaneous UFH (49 events/1131 participants) versus LMWH (66 events/1141 participants), leading to an OR of 0.73 (95% CI 0.50 to 1.07; N = 2272; 7 studies; I^2 = 0%; low-quality evidence; Analysis 2.6). We observed no differences between the VTE at randomisation subgroups 'DVT with/without PE' versus 'DVT without PE' (P = 0.41).

Asymptomatic VTE at three months

There were no episodes of asymptomatic VTE occurring within three months of the commencement of treatment reported by any studies comparing subcutaneous UFH versus LMWH.

Treatment-related morbidity

Minor bleeding

Five studies with a combined total of 2300 participants measured incidence of minor bleeding within the study period (Belcaro 1999; Kearon 2006; Leizorovicz 2011; Lopaciuk 1992; Prandoni 2004). The incidence of minor bleeding was similar for participants treated with subcutaneous UFH (81 events/1147 participants) versus LMWH (83 events/1153 participants), leading to an OR of 0.98 (95% CI 0.71 to 1.37; N = 2300; 5 studies; I^2 = 0%;; Analysis 2.7). We observed no differences between the VTE at randomisation subgroups 'DVTwith/without PE' versus 'DVT without PE' (P = 0.93).

Heparin-induced thrombocytopenia

Three studies with a combined total of 1954 participants measured the incidence of HIT (Kearon 2006; Leizorovicz 2011; Prandoni 2004). The outcome was similar for participants treated with subcutaneous UFH (3 events/972 participants) versus LMWH (2 events/982 participants), leading to an OR of 1.52 (95% CI 0.25 to 9.14; N = 1954; 3 studies; I^2 = 0%; Analysis 2.8). All three studies included participants with PE, so we could not perform subgroup analysis based on VTE at randomisation.

Length of hospital stay

Belcaro 1999 measured days in hospital, but the subcutaneous UFH group received treatment at home, so we could not make a comparison. The mean length of hospital stay in the LMWH group was 5.1 ± 1.0 days.

Quality of life

None of the included studies measured quality of life as an outcome

Subgroup analysis

Data were not available for subgroup analysis by first or recurrent VTE, severity of VTE, age of participants, renal function or underlying pathology of VTE. Additionally, data were not available for subgroup analysis by number of daily subcutaneous heparin injections, type of dose adjustment, initial intravenous bolus heparin given versus not given, concomitant oral anticoagulant use or timing of oral anticoagulant initiation. We report results of subgroup analyses by VTE at randomisation above.

Sensitivity analysis

We performed sensitivity analyses in order to explore the influence of certain factors on effect size. We considered two studies large compared with others (Kearon 2006; Prandoni 2004). Both compared subcutaneous UFH versus LMWH. Exclusion of these

trials from the analysis of outcomes did not influence the results (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.7). We did not analyse the effect of published versus unpublished trials, as no unpublished data were available. Sensitivity of the results to the quality of trials was not feasible, as we judged all but one trial to be at a high risk of bias. Furthermore, we could not perform sensitivity analyses by diagnostic criteria, language of publication or source of funding due to insufficient data.

DISCUSSION

Summary of main results

Symptomatic recurrent VTE at three months

Meta-analyses showed no difference in the rate of symptomatic recurrent VTE at three months between subcutaneous UFH versus IV UFH or LMWH. Our analyses showed little or no statistical heterogeneity between the included studies. When comparing subcutaneous UFH versus LMWH, the subgroup analysis by VTE at randomisation showed no difference between participants that had DVT without PE and those that had DVT with/without PE. Furthermore, we observed no difference when excluding two large studies from the analysis.

Symptomatic recurrent DVT at three months

Meta-analyses showed no difference in the rate of symptomatic recurrent DVT at three months between subcutaneous UFH versus IV UFH or LMWH.

PE at three months

Meta-analyses showed no difference in the rate of PE between subcutaneous UFH and IV UFH nor LMWH. When comparing subcutaneous UFH versus LMWH, subgroup analysis by VTE at randomisation showed no difference between participants that had DVT without PE and those that had DVT with/without PE.

VTE-related mortality at three months

Meta-analyses showed no difference in the rate of VTE-related mortality at three months between subcutaneous UFH versus IV UFH or LMWH. There were no cases of VTE-related mortality in the four studies incorporating participants that had DVT without PE. Furthermore, we observed no difference when excluding two large studies from the analysis.

Major bleeding

Meta-analyses showed no difference in the rate of major bleeding between subcutaneous UFH versus IV UFH or LMWH. When comparing subcutaneous UFH versus LMWH, subgroup analysis by VTE at randomisation showed no difference between participants that had DVT without PE and those that had DVT with/without PE. Furthermore, we observed no difference when excluding two large studies from the analysis.

All-cause mortality

Meta-analyses showed no difference in the rate of all-cause mortality between subcutaneous UFH versus IV UFH or LMWH. When comparing subcutaneous UFH versus LMWH, subgroup analysis by VTE at randomisation showed no difference between participants that had DVT without PE and those that had DVT with/without PE.

Asymptomatic VTE at three months

None of the included studies reported any episodes of asymptomatic VTE occurring within three months of the commencement of treatment.

Treatment-related morbidity

Minor bleeding

Meta-analyses showed no difference in the incidence of minor bleeding between subcutaneous UFH and IV UFH or LMWH. When comparing subcutaneous UFH versus LMWH, subgroup analysis by VTE at randomisation showed no difference between participants that had DVT without PE and those that had DVT with/without PE. Furthermore, we observed no difference when excluding two large studies from the analysis.

Heparin-induced thrombocytopenia

None of the studies comparing subcutaneous UFH versus IV UFH reported any episodes of HIT. Meta-analyses showed no difference in the incidence of HIT between participants treated with subcutaneous UFH versus LMWH. When comparing subcutaneous UFH versus LMWH, subgroup analysis by VTE at randomisation showed no difference between participants that had DVT without PE and those that had DVT with/without PE. Furthermore, we observed no difference when excluding two large studies from the analysis.

Length of hospital stay

One three-armed study, comparing subcutaneous UFH versus IV UFH versus LMWH, measured length of hospital stay associated with each treatment. However, the subcutaneous UFH group received treatment at home, so we could not make a comparison. The mean length of hospital stay was 5.4 ± 1.4 days in the IV UFH and 5.1 ± 1.0 days in the LWMH groups, respectively.

Quality of life

None of the included studies measured quality of life as an outcome.

Overall completeness and applicability of evidence

This review assessed whether subcutaneous UFH reduced the rate of recurrent VTE, VTE-related mortality, major bleeding and all-cause mortality in participants with VTE. Eight studies used IV UFH as the comparator and seven studies used LMWH, while one three-armed trial compared all three of those treatment possibilities. We did not identify trials comparing subcutaneous UFH with other anticoagulant drugs. All trials included participants with deep vein thrombosis. Seven trials excluded people with a PE, four trials included PE participants, and the remaining trials did not clearly describe PE inclusion. With the exception of asymptomatic VTE at three months and health-related quality of life, the included studies measured and reported all of the addressed outcomes. As all the trials had strict inclusion criteria, resulting in an overall participant population with almost identical conditions, statistical heterogeneity was logically low for all outcomes. Furthermore, studies used similar concentrations for each particular drug.

We planned subgroup analyses by first or recurrent VTE, severity, age, renal function, underlying pathology, number of daily subcutaneous heparin injections, type of dose adjustment, initial intravenous bolus heparin given versus not given, concomitant oral anticoagulant use, and timing of oral anticoagulant initiation. However, we could not perform these subgroup analyses because of the lack of participant-level data.

Although many researchers consider DVT and PE to be manifestations of the same disorder, we elected to present them in the form of subgroups, as there is evidence of clinically significant differences between them. Most recurrent events occur at the same site as the original thrombosis (in other words, in a person presenting with a PE, a recurrent event after treatment is much more likely to be another PE). For comparisons and outcomes where subgroup analyses were possible, we did not observe any differences between studies recruiting participants that had DVT without PE and participants that had DVT with/without PE.

The American College of Chest Physicians (ACCP) clinical practice guidelines for the treatment of VTE suggest UFH as the treatment of choice for patients with severe renal failure (Kearon 2012). This is a grade 2C recommendation, based on low-quality evidence that LMWH is associated with increased bleeding in patients with impaired renal function. Only one trial included in our review studied participants with impaired renal function (Leizorovicz 2011), comparing subcutaneous UFH versus LMWH tinzaparin in the treatment of acute DVT. The trial was terminated early due to a difference in mortality that favoured the group treated with UFH. However, rates of major bleeding and recurrent VTE were similar between the two groups.

Quality of the evidence

The risk of bias was high in 15 out of the 16 included studies, reflecting low methodological quality (Figure 2; Figure 3). This was largely due to the lack of blinding in 14 studies, which led to a high risk of performance bias. The risk of detection bias was lower: 8 of the 16 included studies reported that outcomes assessors were blinded to the treatment and adjudicated by a central independent committee. We judged seven studies to be at high risk of attrition bias for failing to account for missing data, one study to be at high risk of selection bias because of insufficient reporting of the methods used to conceal treatment allocation, and another study to be at high risk of reporting bias because it reported a significant result on an outcome that was not pre-specified. We could not investigate publication bias because we could not assess asymmetry in a funnel plot with the limited number of studies included in the meta-analysis.

For all outcomes in both comparisons, we downgraded the quality of the evidence to low due to the high risk of bias within each included study and also due to imprecision stemming from the small number of outcome events, as reflected by the wide confidence intervals.

Potential biases in the review process

The search was as comprehensive as possible, and we are confident that we have included all relevant studies. However, the possibility remains that we missed some relevant trials, particularly in the grey literature (for example conference proceedings). Two review authors independently performed study selection and data extraction in order to minimise bias in the review process. We performed data collection according to the process suggested by Cochrane. We also followed Cochrane processes as described by Higgins 2011 for assessing the risk of bias.

Agreements and disagreements with other studies or reviews

A meta-analysis comparing subcutaneous heparin with intravenous heparin published in 1992 concluded that the subcutaneous mode of administration was more efficacious and less toxic than the intravenous mode of administration (Hommes 1992). Another more recent review of the literature comparing subcutaneous UFH versus subcutaneous LMWH concluded that subcutaneous UFH was an attractive alternative to LWMH for VTE, being "cheap, effective and safe" (Munro 2008).

Since the introduction of LMWH, there has been a shift away from the older and less easy-to-use UFH. Several other meta-analyses of the medical literature have been published over the years, suggesting enhanced efficacy and safety profile for LMWH (Erkens 2010; Gould 1999).

AUTHORS' CONCLUSIONS

Implications for practice

Low-quality evidence suggests there is no difference in effectiveness between subcutaneous UFH, IV UFH and LMWH for preventing recurrent VTE at three months, VTE-related mortality, major bleeding and all-cause mortality. Therefore, for people with difficult venous access or people who could be treated at home, subcutaneous UFH appears to be an acceptable alternative to IV UFH. Futhermore, in patients with severe renal impairment, subcutaneous UFH can be used instead of LMWH.

Implications for research

Further research is required to consolidate non-monitored subcutaneous administration of UFH in the setting of VTE. Future research should target specific patient groups, e.g. patients with chronic kidney disease and elderly patients, and specific VTE states (e.g. DVT versus PE), and researchers should analyse data separately for their response to the proposed intervention. Finally, studies should evaluate cost-effectiveness, comparing continuous infusions of UFH versus subcutaneous administration of LMWH.

ACKNOWLEDGEMENTS

We would like to thank Dr M Vardi, Dr E Zittan, and Dr H Bitterman for their contributions to previous versions of this review.

We would like to thank Dr K Welch for searching the Cochrane Vascular Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (www.thecochranelibrary.com). We would also like to thank Dr M Stewart, Managing Editor of Cochrane Vascular for her assistance and advice in completing this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Andersson 1982

Methods	**Study design**: open randomised controlled trial **Duration of intervention**: at least 5 days to INR target **Duration of follow-up**: acute phase only **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute DVT **Country**: Sweden **Number of study centres**: 3 **Setting**: hospital **Number**: 141 (SC UFH group 72; IV UFH group 69) **Age mean (range)**: SC UFH group 64 years (23 to 88); IV UFH group 64 years (20 to 88) **Sex (M/F)**: SC UFH group 47/25; IV UFH group 41/28

Andersson 1982 *(Continued)*

	Inclusion criteria: clinical signs of acute DVT **Exclusion criteria**: not stated **Diagnostic criteria**: phlebography, venous occlusion plethysmography, thermography
Interventions	**Intervention (route, total dose/day, frequency)**: IV UFH bolus dose (sodium heparin) (5000 IU/mL) followed by SC UFH (25000 IU/mL) twice daily aPTT adjusted + warfarin **Control (route, total dose/day, frequency)**: IV UFH bolus dose (sodium heparin) (5000 IU/mL) followed by continuous IV UFH aPTT adjusted + warfarin **Treatment before study**: NA **Titration period**: NA
Outcomes	**Primary outcome**: therapeutic efficacy with repeat imaging **Secondary outcomes**: bleeding, pulmonary emboli, aPTT, heparin dose
Notes	**Stated aim of the study**: assess therapeutic effect and number of complications in the two groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random but no description of randomisation method provided
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding provided Different methods of administration meant adequate blinding was most likely not achieved "Intravenous infusions were administered by mobile infusion pumps" "Subcutaneous injections were given into the anterior abdominal wall using a 23 gauge needle"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used – no description of blinding outcome assessors Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – no description of blinding outcome assessors Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data not used - not meeting ISTH definition Minor bleeding: data not used - not meeting definition of minor bleeding VTE-related mortality: data used

Andersson 1982 *(Continued)*

		All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	High risk	40 participants (out of 141) withdrawn from the study "due to inabilities to achieve these investigations during weekends and holidays, technical reasons or because some patients refused further investigations" 19 participants withdrawn from the subcutaneous group and 21 participants withdrawn from the intravenous group. However, the number of participants withdrawn for each reason is not presented. No deaths were reported as occurring during the course of the study
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	No evidence of other biases

Belcaro 1999

Methods	**Study design**: open randomised aPTT-controlled trial **Duration of intervention**: 3 months for SC heparin; until INR target in LMWH and IV heparin **Duration of follow-up**: 3 months **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute DVT **Country**: Italy (Chieti and Pescara), UK **Number of study centres**: 3 **Setting**: SC UFH - outpatient; LMWH - out/inpatient; IV UFH - inpatient **Number**: 325 randomised, 294 completed the study (SC UFH 99; LMWH 98; IV UFH 97) **Age (mean ± SD)**: SC UFH 54 ± 9 years; LMWH 54 ± 11 years; IV UFH 53 ± 10 years **Sex (M/F)**: SC UFH 52/47; LMWH 54/44; IV UFH 57/40 **Inclusion criteria**: acute proximal DVT diagnosed by colour duplex ultrasonography **Exclusion criteria**: 2 or more previous episodes of DVT or PE, current active bleeding, active ulcers, bleeding or coagulation disorder, concurrent PE, treatment for DVT with standard heparin > 48 h, home treatment not possible, neoplasia requiring surgery or chemotherapy in three months, likelihood of low compliance, pregnancy, platelets < 100,000 × 10^9/L **Diagnostic criteria**: colour duplex
Interventions	**Intervention (route, total dose/day, frequency)**: SC heparin (12,500 IU twice daily), fixed dose (no oral anticoagulation) administered exclusively at home

Belcaro 1999 *(Continued)*

	Control (route, total dose/day, frequency): group 1: LMWH (100 Axa IU/kg twice daily) administered primarily at home + warfarin; group 2: IV bolus (5000 IU) followed by continuous IV UFH aPTT adjusted + warfarin **Treatment before study**: NA
Outcomes	Outcomes not specified as primary or secondary **Outcomes**: symptomatic or asymptomatic recurrent DVT or DVT extension at 3 months, bleeding during the administration of the study drug, PE, length of stay in hospital, number of participants treated directly at home without admission
Notes	**Stated aim of the study**: to compare intravenous standard heparin (in hospital) with oral anticoagulant treatment to LMWH and oral anticoagulant treatment administrated primarily at home, to SC heparin administered at home

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random but no description of randomisation method provided
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Use of open study design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data not used – results for symptomatic, asymptomatic and extended VTE not presented separately Recurrent DVT at 3 months: data not used – see recurrent VTE at 3 months PE – excluding PE found at autopsy: data used – "All reported outcome events were reviewed by a central panel including all monitors and, by form evaluation, by five external reviewers unaware of the treatments assigned and the patient's identity" Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: data not used – see recurrent VTE at 3 months Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data used Minor bleeding: data used VTE-related mortality: data used All-cause mortality: data not used – unclear how many deaths occurred in each group

Belcaro 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	31 (out of 325) participants were withdrawn from the study Although the paper states that six participants died during the course of the study – all other withdrawals are unaccounted for
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Unclear risk	Different groups were treated in different locations with groups 1 and 2 receiving different treatments in hospital and group 3 receiving treatment at home

Bentley 1980

Methods	**Study design**: open randomised controlled trial **Duration of intervention**: 7 days to INR target **Duration of follow-up**: 7 days **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute DVT **Country**: UK **Number of study centres**: 1 **Setting**: inpatient **Age (mean ± SD)**: SC UFH group 60.49 ± 14.32 years; IV UFH group 58.18 ± 12.66 years **Sex (M/F)**: not specified but describes "well matched for age, sex ..." **Inclusion criteria**: acute calf DVT diagnosed by venography **Exclusion criteria**: contra-indication to heparin, thrombus extension < 5 cm **Diagnostic criteria**: venography
Interventions	**Intervention (route, total dose/day, frequency)**: SC UFH (calcium heparin), initial dose 40,000 IU/day followed by aPTT-adjusted dose twice daily + warfarin **Control (route, total dose/day, frequency)**: IV UFH (sodium heparin), initial dose 40,000 IU/day followed by aPTT-adjusted continuous dose + warfarin **Treatment before study**: NA
Outcomes	Outcomes not specified as primary or secondary **Outcomes**: cutaneous haematoma, macroscopic haematuria, major bleeding, DVT extension, new or extended PE, aPTT, heparin level
Notes	**Stated aim of the study**: to compare the safety and efficacy of IV and SC heparin
Risk of bias	

Bentley 1980 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random but no description of randomisation method provided
Allocation concealment (selection bias)	Low risk	"Patients were randomised using sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding provided Different methods of heparin administration – intravenous compared to subcutaneous – probably prevented adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used – no description of blinding outcome assessors Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – no description of blinding outcome assessors Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data not used - not meeting ISTH definition Minor bleeding: data not used - not meeting definition of minor bleeding VTE-related mortality: data used All-cause mortality: data used Description of blinding outcome assessors for PE
Incomplete outcome data (attrition bias) All outcomes	High risk	The study states 3 participants (out of 100) were withdrawn from the study – but from which groups is unclear Later in the paper it states that the heparin treatment of 6 participants was halted (2 in SC group and 4 in IV group) However, all participants are included in the final analysis of venographic results without further explanation No deaths were reported as occurring during the course of the study
Selective reporting (reporting bias)	Low risk	Study states estimations of platelet count; haemoglobin and hematocrit were made at the beginning, middle and end of the trial period – however – results are only presented for participants with minor bleeds. Nevertheless these were not outcomes of our review and therefore the study was judged to be at low risk of reporting bias.
Other bias	Low risk	No evidence of other biases

Doyle 1987

Methods	**Study design**: open randomised controlled trial **Duration of intervention**: 10 days **Duration of follow-up**: 12 months **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute DVT **Country**: Canada **Number of study centres**: 1 **Setting**: inpatients **Number**: 103 SC UFH 51; IV UFH 52 **Age mean (range)**: SC UFH 66.6 years (31 to 96); IV UFH 64.6 (25 to 94) years **Sex (M/F)**: SC UFH 23/28; IV UFH 32/20 **Inclusion criteria**: acute proximal or calf DVT diagnosed by venography **Exclusion criteria**: clinically suspected PE, active peptic ulceration, bleeding disorder, no informed consent **Diagnostic criteria**: venography
Interventions	**Intervention (route, total dose/day, frequency)**: SC UFH (calcium heparin), initial dose 15,000 IU, then twice daily, aPTT adjusted + warfarin **Control (route, total dose/day, frequency)**: IV UFH (calcium heparin), initial dose 5,000 IU, then continuous, aPTT adjusted + warfarin **Treatment before study**: NA
Outcomes	**Primary outcome**: PE **Secondary outcomes**: other lung scan abnormalities, bleeding, leg symptoms, death
Notes	**Stated aim of the study**: to determine the efficacy and safety of adjusted SC calcium heparin compared with continuous IV calcium heparin as the initial treatment for acute DVT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random but no description of randomisation method provided
Allocation concealment (selection bias)	Low risk	use of "sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Use of "open" trial design

Doyle 1987 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used - the scintigrams were interpreted in random order by 2 experienced experimental observers who were blinded to the method of treatment Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – see recurrent VTE at 3 months Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data used Minor bleeding: data used VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 participants (out of 103) were withdrawn from the study – 4 in SC group; 3 in the IV group Reasons for withdrawal were clearly presented: "2 had major bleeding; 1 refused the scan; 1 required surgery and 3 could not have the scans for technical reasons" During follow-up 10 participants died – none from PE
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other biases

Faivre 1987

Methods	**Study design**: randomised controlled trial **Duration of intervention**: 10 days **Duration of follow-up**: 10 days **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: French
Participants	**Who participated**: people with acute DVT and PE **Country**: France **Number of study centres**: 1 **Setting**: inpatient

Faivre 1987 *(Continued)*

	Number: 68 SC UFH 35; SC LMWH 33 (number evaluated: 59 SC UFH 29; SC LMWH 30)
	Age (mean ± SD) : SC UFH 63.6 ± 16.2 years; SC LMWH 65.6 ± 14.8 years
	Sex (M/F): 39/29
	Inclusion criteria: acute DVT or PE diagnosed with phlebography or perfusion-ventilation scan
	Exclusion criteria: over 2 weeks of symptoms, massive PE
	Diagnostic criteria: phlebography and lung scan
Interventions	**Intervention (route, total dose/day, frequency)**: SC UFH (calcium heparin) 500 IU/kg/day in form of twice daily injections, aPTT adjusted
	Control (route, total dose/day, frequency): SC LMWH 750 anti-Xa/kg/day in form of twice daily injections
	Treatment before study: NA
Outcomes	Outcomes not specified as primary or secondary
	Outcomes: DVT extension, bleeding
Notes	**Stated aim of the study**: to assess the efficacy and safety of CY222 for the treatment of DVT compared with SC heparin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random but no description of randomisation method provided
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding provided and although both treatments were administered subcutaneously, the authors state that in the CY222 group participants received a fixed dose of (750 U anti-Xa IC/kg/24 h) whist in the unfractionated heparin group dosage was adjusted to maintain partial thromboplastin time, making it unlikely participant and personnel were adequately blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: NA Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: NA Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data not used - not meeting ISTH definition Minor bleeding: NA

Faivre 1987 *(Continued)*

		VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	High risk	9 participants (out of 68) were withdrawn from the study In the CY22 group 3 participants withdrew (cardiac insufficiency, migration of Greenfield filter) In the SC group 6 participants withdrew (3 retroperitoneal haematoma; 3 recurrent PE)
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other biases

Holm 1986

Methods	**Study design**: double-blind randomised controlled trial **Duration of intervention**: 7 days **Duration of follow-up**: 7 days **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute DVT **Country**: Norway **Number of study centres**: 1 **Setting**: inpatients **Number**: 56 (SC UFH 27; SC LMWH 29) **Age (mean ± SD)**: SC UFH 60 ± 15.8 years; SC LMWH 61 ± 15.3 years **Sex (M/F)**: 33/23 (SC UFH 17/10; SC LMWH 16/13) **Inclusion criteria**: acute DVT below the groin diagnosed by phlebography, with symptoms for fewer than 14 days **Exclusion criteria**: PE, pregnancy, history of cerebral haemorrhage, surgery in previous 6 days, diastolic BP > 115 mmHg, retinal haemorrhage, impaired renal function, impaired PT **Diagnostic criteria**: phlebography
Interventions	**Intervention (route, total dose/day, frequency)**: IV continuous infusion UFH for 24 hours, followed by SC UFH 10,000-15,000 IU twice daily, anti-Xa adjusted + warfarin **Control (route, total dose/day, frequency)**: IV continuous infusion UFH for 24 hours, followed by SC LMWH 5000-7500 IU twice daily, anti-Xa adjusted + warfarin **Treatment before study**: NA

Holm 1986 *(Continued)*

Outcomes	Outcomes not specified as primary or secondary **Outcomes**: DVT extension, new PE, bleeding, leg pain, death, haemoglobin, platelets
Notes	**Stated aim of the study**: to compare subcutaneous heparin and LMWH for the treatment of DVT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random but no description of randomisation method provided
Allocation concealment (selection bias)	High risk	"the vials [of low molecular weight or unfractionated heparin] had been randomised in advance and numbered consecutively, the number of patient admission determining the number of vial used" It is possible personnel had access to the order of the vials
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Paper states only "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used – no description of blinding outcome assessors Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – no description of blinding of outcome assessors Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data not used - not meeting ISTH definition Minor bleeding: data not used - not meeting definition of minor bleeding VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants (out of 56) were withdrawn from the trial – 2 from the LMWH group; 1 from UFH group Reasons for withdrawals are clearly presented: Reversal of DVT diagnosis; incorrect injection of ordinary heparin and suspected cerebral haemorrhage No deaths were reported as occurring during the course of the study

Holm 1986 *(Continued)*

Selective reporting (reporting bias)	High risk	Study presents results for leg pain "leg pain disappeared somewhat quicker in patients receiving LH"; however, pain measures were not presented as an outcome in the Methods section In addition, the paper states that "there was no drop in platelet count or haemoglobin concentration"; however, how these parameters were measured is also unreported in the Methods section
Other bias	Low risk	No significant evidence of other biases; however, one patient was included twice (once in each group) and one patient transferred to the UFH group and so was not included in the final analysis This could potentially be considered an as-treated analysis, and as such it may have potentially introduced selection bias; however, as only one patient was affected the potential risk of bias was considered small and was deemed unlikely to have significantly affected the results of the study

Hull 1986

Methods	**Study design**: double-blind randomised controlled trial **Duration of intervention**: 10 days **Duration of follow-up**: 3 months **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute DVT **Country**: Canada **Number of study centres**: 1 **Setting**: inpatients **Number**: 115 **Age (< 60 years / > 60 years)**: SC UFH 10/4; 7 IV UFH 11/47 **Sex (M/F)**: SC UFH 27/30; IV UFH 28/30 **Inclusion criteria**: acute proximal (± calf) DVT diagnosed by venography **Exclusion criteria**: active bleeding, contraindication to heparin, already on heparin, no outpatient follow-up available **Diagnostic criteria**: venography
Interventions	**Intervention (route, total dose/day, frequency)**: IV UFH 5000 IU bolus followed by SC UFH 15000 twice daily, aPTT adjusted + warfarin **Control (route, total dose/day, frequency)**: IV UFH 5000 IU bolus followed by continuous IV UFH aPTT adjusted + warfarin **Treatment before study**: NA
Outcomes	Outcomes not specified as primary or secondary

Hull 1986 *(Continued)*

	Outcomes: recurrent DVT, PE, bleeding, aPTT, death
Notes	**Stated aim of the study**: to compare continuous IV heparin to intermittent SC heparin for the initial treatment of proximal DVT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer generated prescribed randomised arrangement was used to assign patients"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"those to receive continuous IV heparin were ... started on a continuous IV infusion … and placebo SC injections" "those to receive SC heparin were given SC heparin injections … and IV placebo infusions" "to prevent un-blinding … masked pre-labelled syringes and IV packs were used" "to prevent un-blinding on the basis of knowledge of heparin clearance … all dose adjustments and anticoagulant monitoring … were [done at a] daily mid interval measurement"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used - "[d]iagnostic tests were interpreted independently and without knowledge of the results of the other tests or the patient's clinical state or the treatment group to which the patient had been assigned" Recurrent DVT at 3 months: data used – see recurrent VTE at 3 months PE – excluding PE found at autopsy: data used – See recurrent VTE at 3 months Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data used Minor bleeding: data used VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	Low risk	0 participants (out of 115) were withdrawn from the study "[A]ll patients were followed during primary therapy and for three months during long term therapy and none were lost to follow up" 6 participants died in the subcutaneous group, 2 from VTE-related causes; 3 participants died in the intravenous group, none from VTE-related causes

Hull 1986 *(Continued)*

Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	No evidence of other biases

Kearon 2006

Methods	**Study design**: open-label, adjudicator-blinded randomised controlled trial **Duration of intervention**: 5 days to INR target **Duration of follow-up**: 3 months **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute DVT or PE **Country**: Canada and New Zealand **Number of study centres**: 6 **Setting**: inpatients and outpatients **Number**: 708 (SC UFH 355; SC LMWH 353) **Age (mean ± SD)**: SC UFH 60 ± 17 years; SC LMWH 60 ± 16 years **Sex (M/F)**: SC UFH 182/173; SC LMWH 206/147 **Inclusion criteria**: 18 years or older with newly diagnosed DVT of the legs or PE diagnosed by compression ultrasonography or by venography, and by a high probability ventilation-perfusion lung scan, by non diagnostic findings on lung scan accompanied by diagnostic findings for DVT, or by computed tomographic angiography **Exclusion criteria**: contraindication to subcutaneous therapy such as shock or major surgery in the past 48 hours, active bleeding, a life expectancy of less than 3 months, previous acute treatment for venous thromboembolism for more than 48 hours, receiving long-term anticoagulant therapy, contraindication to heparin or to radiographic contrast, creatinine level of greater than 200 µmol/L (2.3 mg/dL), pregnant, enrolled in a competing study, unable to have follow-up assessments because of geographic inaccessibility **Diagnostic criteria**: compression ultrasonography or venography, and high probability ventilation-perfusion lung scan, non-diagnostic findings on lung scan accompanied by diagnostic findings for deep vein thrombosis, or computed tomographic angiography **Type of VTE**: 571 DVT/174 PE
Interventions	**Intervention (route, total dose/day, frequency)**: unmonitored SC UFH, initial 333 IU/kg followed by 250 IU/kg twice daily + warfarin **Control (route, total dose/day, frequency)**: SC LMWH 100 IU/kg twice daily + warfarin **Treatment before study**: NA
Outcomes	**Primary outcomes**: the primary analysis for efficacy was the absolute difference in the proportion of eligible participants who had recurrent venous thromboembolism at 3 months. The primary analysis

Kearon 2006 *(Continued)*

	for safety was the absolute difference in the proportion of participants who received at least 1 dose of study drug who had an episode of major bleeding within 10 days of randomisation **Secondary outcomes**: recurrent VTE at 10 days, major or minor bleeding, death, aPTT
Notes	**Stated aim of the study**: to determine if fixed-dose, weight-adjusted, subcutaneous unfractionated heparin is as effective and safe as low molecular-weight heparin for treatment of venous thromboembolism

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was computer generated with block sizes of 2 or 4"
Allocation concealment (selection bias)	Low risk	"[C]linical centres telephone an automated centralised system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Use of "open-label" study design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used - all outcome events and deaths were classified by a central adjudication committee whose members were unaware of treatment assignment Recurrent DVT at 3 months: data used – see recurrent VTE at 3 months PE – excluding PE found at autopsy: data used – see recurrent VTE at 3 months Incidence of heparin-induced thrombocytopenia: data used – see recurrent VTE at 3 months Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data used Minor bleeding: data used VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 participants (out of 708) were withdrawn from the study – 10 in the UFH group; 1 in the LMWH group Reasons for withdrawals were clearly reported and the asymmetry in the withdrawals did not appear to be caused by the different treatment methods: UFH – 4 participants were receiving long-term anticoagulant therapy; 3 diagnosis of VTE were reversed; 1 randomisation error; 1 withdrawal of consent and 1 withdrawal by physician LMWH – 1 withdrawal of consent

Kearon 2006 *(Continued)*

		During follow-up there were 18 deaths in the UFH group (1 from bleeding) and 22 deaths in the LMWH group (3 from PE and 1 from bleeding)
Selective reporting (reporting bias)	Low risk	Protocol available - no evidence of selective reporting
Other bias	Low risk	No significant evidence of other biases - 5 participants who did not receive the study drug were not included in the final analysis of either safety or efficacy – something which could be considered an 'as-treated' analysis that potentially introduced selection bias; however, the number of participants affected was considered too small to have had a significant impact on the results

Krähenbühl 1979

Methods	**Study design**: randomised controlled trial **Duration of intervention**: 7 days **Duration of follow-up**: 6 weeks **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: French
Participants	**Who participated**: people with acute DVT of the lower limb **Country**: Switzerland **Number of study centres**: 1 **Setting**: inpatients **Number**: 48 (SC UFH 23; IV UFH 25) **Age**: not stated **Sex (M/F)**: SC UFH 18/5; IV UFH 13/12) **Inclusion criteria**: DVT of lower limbs diagnosed by phlebography or colour duplex US, with symptoms < 1 week **Exclusion criteria**: none stated **Diagnostic criteria**: phlebography or colour duplex ultrasound
Interventions	**Intervention (route, total dose/day, frequency)**: IV bolus UFH (sodium heparin) 5000 IU, followed by SC UFH 15,000U/day twice daily (aPTT adjusted) **Control (route, total dose/day, frequency)**: IV bolus UFH (sodium heparin) 5000 IU followed by IV continuous UFH (aPTT adjusted) **Treatment before study**: NA
Outcomes	Outcomes not specified as primary or secondary **Primary Outcomes**: symptoms duration, DVT extension, PE, aPTT

Krähenbühl 1979 *(Continued)*

Notes	**Stated aim of the study**: to compare subcutaneous heparin and intravenous heparin for the treatment of deep vein thrombosis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Drawing of lots"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding provided Different methods of heparin administration – intravenous compared to subcutaneous – probably prevented adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used – no description of blinding outcome assessors Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – no description of blinding outcome assessors Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data not used - not meeting ISTH definition Minor bleeding: data not used - not meeting definition of minor bleeding VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 24 participants (out of 48) received a second phlebograph: reasons for this loss are not clearly presented in the article
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	No evidence of other biases

Leizorovicz 2011

Methods	**Study design**: international, multicentre, centrally randomised, open, parallel-group study with blinded adjudication **Duration of intervention**: 90 ± 5 days

Leizorovicz 2011 *(Continued)*

	Duration of follow-up: NA **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people aged ≥ 75 years with creatinine clearance (CrCl) ≤ 60 mL/min or people aged ≥ 70 years with a CrCl of ≤ 30 mL/min (calculated using the Cockcroft–Gault formula) and with an acute, objectively confirmed (by compression ultrasonography or venography) lower limb DVT which required treatment **Countries**: Belgium; France; Germany; Spain; Serbia; Croatia; Romania and Poland **Number of study centres**: 8 **Setting**: inpatients at the time of randomisation; however, participants could be followed on a daily basis in or out of hospital after this point **Number**: 539 **Age (< 60 years/ > 60 years)**: SC UFH 0/270; tinzaparin 0/269 **Sex (M/F)**: SC UFH 102/168; tinzaparin 92/177 **Inclusion criteria**: objectively confirmed symptomatic proximal or distal DVT (or objectively confirmed asymptomatic DVT if proximal and associated with a PE) and provision of written informed consent **Exclusion criteria**: received treatment doses of heparins or thrombolytic agents within the previous 4 weeks (excluding the last 36 h) prior to randomisation; received oral anticoagulation within the preceding week; planned use of high doses of acetylsalicylic acid (ASA) (> 300 mg/day) or a non-steroidal anti-inflammatory drug (NSAID); requirement for thrombolytic therapy; end stage renal disease requiring dialysis; hepatic insufficiency (INR ≥ 1.5); bacterial endocarditis; planned epidural or spinal anaesthesia; planned surgery or recent surgery (within 2 weeks); thrombocytopenia (< 100 x 10^9/L); severe uncontrolled hypertension, overt bleeding and recent stroke **Diagnostic criteria**: compression ultrasonography or venography
Interventions	**Intervention (route, total dose/day, frequency)**: tinzaparin (SC, 175 IU/kg, once daily) **Control (route, total dose/day, frequency)**: UFH (IV, 50 IU/kg bolus followed by SC, 400–600 IU/kg, twice daily which was then adjusted by APTT according to local practice) **Treatment before study**: NA
Outcomes	**Primary outcomes**: clinically relevant bleedings (CRBs) by day 90 ± 5 **Secondary outcomes**: occurrence of symptomatic recurrent VTE prior to day 90 ± 5 and major and minor bleedings prior to day 90 ± 5 **Tertiary outcomes**: CRBs during the SC treatment phase, death from any cause prior to day 90 ± 5 and heparin-induced thrombocytopenia
Notes	**Stated aim of the study**: to compare the safety profile of full weight-based unadjusted-dose tinzaparin (Innohep, LEO Pharma, Ballerup, Denmark) vs activated partial thromboplastin time (APTT)-adjusted UFH as initial treatment of elderly participants with impaired renal function and acute DVT

Risk of bias

Bias	Authors' judgement	Support for judgement

Leizorovicz 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Treatment assignment was pre-planned according to a computer generated randomisation sequence"
Allocation concealment (selection bias)	Low risk	"Central telephone randomisation" However, the paper also states: "No allocation concealment mechanism was attempted as the study was open. But care was taken to ensure that outcome assessors and data analysts were kept blinded to the allocation" This statement appears to be in contradiction with the description of central telephone randomisation and so it was assumed that in this context 'allocation concealment' referred to the blinding of participants and personnel, as an open study design does not preclude adequate allocation concealment - this assumption was also more consistent with the reference to the blinding of outcome assessors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Use of an "open" study design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used - care was taken to ensure that outcome assessors and data analysts were kept blinded to the allocation Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – see recurrent VTE at 3 months Incidence of heparin-induced thrombocytopenia: data used – see recurrent VTE at 3 months Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data used Minor bleeding: data used VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants (out of 539) were withdrawn from the study for reasons that were clearly presented: 2 from the tinzaparin group as "no treatment [was] taken" 3 from the unfractionated heparin group 2 because of a withdrawal of consent and 1 because "no treatment [was] taken" During the course of the study 48 participants died: 31 participants from the tinzaparin group and 17 from the unfractionated heparin group The large imbalance in mortality between the treatment groups has been addressed by the authors and appears to have been caused by an increased prevalence of specific risk factors in the tinzaparin group including presence of

Leizorovicz 2011 *(Continued)*

		infectious disease; ongoing malignancy; cardiac insufficiency; stratum of renal impairment and leg paralysis, which all correlated significantly with mortality Only 4 deaths could be directly attributed to the heparin treatment 3 in the tinzaparin group – 2 from bleeding and 1 from pulmonary embolism 1 in the unfractionated heparin group also from pulmonary embolism
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	No significant evidence of other biases - 3 participants transferred from the unfractionated heparin to the tinzaparin group and were included in the tinzaparin group for the analysis of adverse effects – something which constitutes an 'as treated' analysis and as such potentially introduced selection bias; however, the number of participants affected was considered too small to significantly affect the results

Lopaciuk 1990

Methods	**Study design**: open randomised controlled trial **Duration of intervention**: 7 days **Duration of follow-up**: 3 months **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: Polish
Participants	**Who participated**: people with acute proximal or calf DVT (with or without PE) **Country**: Poland **Number of study centres**: 5 **Setting**: inpatients **Number**: 94 (SC UFH 48; IV UFH 46) **Age (mean ± SD)**: SC UFH 53.6 ± 13.1 years; IV UFH 50.5 ± 16.9 years **Sex (M/F)**: SC UFH 23/25; IV UFH 24/22 **Inclusion criteria**: calf or proximal DVT diagnosed by phlebography, age 20 to 79 years **Exclusion criteria**: PE necessitating thrombolysis, gastric or duodenal ulcer **Diagnostic criteria**: phlebography **Type of VTE**: DVT
Interventions	**Intervention (route, total dose/day, frequency)**: bolus IV UFH (sodium heparin) 5000 IU, followed by SC UFH 500 IU/kg/day twice daily, aPTT adjusted + sintron (after 7 days) **Control (route, total dose/day, frequency)**: bolus IV UFH (sodium heparin) 5000 IU, followed by continuous IV UFH aPTT adjusted + sintron (after 7 days)

Lopaciuk 1990 *(Continued)*

	Treatment before study: NA
Outcomes	Outcomes not specified as primary or secondary **Outcomes**: DVT extension, aPTT, platelets, PE, bleeding, death
Notes	**Stated aim of the study**: to compare efficacy and safety of SC heparin versus IV heparin for DVT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random but no description of randomisation method provided
Allocation concealment (selection bias)	Low risk	Use of "sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding provided Different methods of heparin administration – intravenous compared to subcutaneous – probably prevented adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used – no description of blinding outcome assessors Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – no description of blinding outcome assessors Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data used Minor bleeding: data used VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants (out of 94) were withdrawn from the study Reasons for withdrawals are clearly presented: Intravenous group – 1 patient died following a pulmonary embolism Subcutaneous group – 1 patient was withdrawn because of bleeding Inclusion of these participants into calculations does not change the results and they participants are correctly included in the analysis of bleeding and thrombotic complications

Lopaciuk 1990 *(Continued)*

Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	No evidence of other biases

Lopaciuk 1992

Methods	**Study design**: open, stratified randomised controlled trial with blind evaluation of phlebographic results **Duration of intervention**: 10 days **Duration of follow-up**: 3 months **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute proximal or calf DVT **Country**: Poland **Number of study centres**: 6 **Setting**: inpatients **Number**: 149 (SC UFH 75 (3 excluded from analysis); SC LMWH 74) **Age (mean ± SD)**: SC UFH 47.8 ±15.4 years; SC LMWH 49.1 ± 15.4 years **Sex (M/F)**: SC UFH 42/30; SC LMWH 39/35 **Inclusion criteria**: calf or proximal DVT diagnosed by phlebography, symptoms shorter than 10 days **Exclusion criteria**: clinically suspected PE, phlegmasia caerulea dolens, treatment with anticoagulation prior to enrolment, VTE in previous 2 years, surgery or trauma in recent 3 days, contraindication to heparin, pregnancy, ATIII deficiency **Diagnostic criteria**: phlebography (blind evaluation of phlebographic results)
Interventions	**Intervention (route, total dose/day, frequency)**: bolus IV UFH 5000 IU, followed by SC UFH 250 IU/kg twice daily, aPTT adjusted + sintron **Control (route, total dose/day, frequency)**: SC LMWH 225 IU/kg twice daily, fixed dose + sintron **Treatment before study**: NA
Outcomes	Outcomes not specified as primary or secondary **Outcomes**: DVT extension, recurrent DVT, PE, bleeding, death
Notes	**Stated aim of the study**: to determine the efficacy and safety of subcutaneous LMWH compared with SC UFH as the initial treatment of DVT of the lower limbs

Risk of bias

Bias	Authors' judgement	Support for judgement

Lopaciuk 1992 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	States random but no description of randomisation method provided
Allocation concealment (selection bias)	Low risk	Use of "sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Use of "open" study design
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used – Outcome assessors blinded for assessment of recurrent DVT "pre and post-treatment phlebograms were assessed blindly" - but no description of blinding of assessors for PE is provided Recurrent DVT at 3 months: data used – see recurrent VTE at 3 months PE – excluding PE found at autopsy: data used – see recurrent VTE at 3 months Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data used Minor bleeding: data used VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants (out of 149) were withdrawn from the trial Reasons for withdrawals are clearly presented: UFH group - 1 patient had a recent history of DVT; 1 patient was diagnosed with antithrombin III deficiency and 1 patient developed major bleeding and was withdrawn from the study; however, their results did appear in the final analysis During follow-up 1 patient from the UFH group died from renal failure
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other biases

Peternel 2002

Methods	**Study design**: open, randomised controlled trial **Duration of intervention**: to INR target **Duration of follow-up**: 7 days

Peternel 2002 *(Continued)*

	Run-in period: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute proximal DVT **Country**: Slovenia **Number of study centres**: 1 **Setting**: inpatients **Number**: 59 (SC UFH 28; SC LMWH 31) **Age (mean ± SD)**: SC UFH 68 ± 13 years; SC LMWH 69 ±14 years **Sex (M/F)**: SC UFH 15/13; SC LMWH 17/14 **Inclusion criteria**: proximal DVT diagnosed by ultrasound duplex **Exclusion criteria**: anticoagulant treatment with heparin or coumarins in the period of 10 days before admission, clinically significant pulmonary embolism or pregnancy **Diagnostic criteria**: ultrasound duplex
Interventions	**Intervention (route, total dose/day, frequency)**: bolus IV UFH, followed by SC UFH twice daily or TID, aPTT adjusted + warfarin **Control (route, total dose/day, frequency)**: SC LMWH 200 IU/kg 4 times daily + warfarin **Treatment before study**: NA
Outcomes	Outcomes not specified as primary or secondary **Outcomes**: major bleeding, death, aPTT, haemostatic markers (F1+2, TAT, D-dimer)
Notes	**Stated aim of the study**: to compare these markers in the acute phase of DVT during treatment either with subcutaneous aPTT-adjusted UFH or with weight-adjusted LMWH in order to estimate control of haemostatic system activation during both regimens

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random but no description of randomisation method provided
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding provided Different numbers of injections at different times – probably prevented adequate blinding UFH – 1 bolus of heparin given intravenously followed by 2-3 subcutaneous injections daily LWMH – 1 subcutaneous injection daily

Peternel 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: NA Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: NA Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data not used - not meeting ISTH definition Minor bleeding: data not used - not meeting definition of minor bleeding VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	High risk	Many of the 59 participants were withdrawn from the study; however, exact numbers withdrawn and from which group they were withdrawn are not presented in the paper Reasons for withdrawal are also not clearly identified – the paper does state that 2 participants died and other participants were withdrawn when INR > 2 for 2 days; however, if all participants were withdrawn for this reason is unclear
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other biases

Pini 1990

Methods	**Study design**: open randomised controlled trial **Duration of intervention**: 7 days **Duration of follow-up**: 7 days **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute DVT **Country**: Italy **Number of study centres**: 1 **Setting**: inpatients **Number**: 271(SC UFH 138; IV UFH 133)

Pini 1990 *(Continued)*

	Age mean (range): SC UFH 63.4 (16 to 87) years; IV UFH 60.9 (11 to 86) years **Sex (M/F)**: SC UFH 83/55; IV UFH 72/61 **Inclusion criteria**: acute DVT diagnosed with strain-gauge plethysmography or venography **Exclusion criteria**: bleeding disorder, abnormal results in haemostatic function screening tests, active peptic disease, on heparin treatment + acenocoumarol **Diagnostic criteria**: plethysmography or venography in diagnosis not concluded
Interventions	**Intervention (route, total dose/day, frequency)**: SC UFH (calcium heparin) 250 U/kg twice daily + acenocoumarol **Control (route, total dose/day, frequency)**: IV UFH (sodium heparin bolus) followed by continuous IV UFH 500 U/Kg/day + acenocoumarol **Treatment before study**: NA
Outcomes	Outcomes not specified as primary or secondary **Outcomes**: DVT extension, PE, death, bleeding
Notes	**Stated aim of the study**: to compare IV and SC heparin for acute DVT in a large population study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned by computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding provided Different methods of heparin administration – intravenous compared to subcutaneous – probably prevented adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used – no description of blinding outcome assessors Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – no description of blinding outcome assessors Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data used Minor bleeding: data used VTE-related mortality: data used

Pini 1990 *(Continued)*

		All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants (out of 271) who were withdrawn from the study is not presented The study states that 23 participants were reported as not undergoing strain gauge plethysmography (SGP) but which group they came from is omitted as is weather any other participants were withdrawn – as only a subset of participants (251) underwent SGP – is unclear 4 participants in the SC group died (1 from PE and 1 from cerebral haemorrhage; 2 participants died in the intravenous group 1 from PE and 1 from pulmonary haemorrhage
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other biases

Prandoni 2004

Methods	**Study design**: open randomised controlled trial **Duration of intervention**: 5 days to INR **Duration of follow-up**: 3 months **Run-in period**: NA **Intention-to-treat analysis**: yes **Language of publication**: English
Participants	**Who participated**: people with acute VTE (DVT + PE) **Number of study centres**: 19 **Setting**: inpatients **Number**: 720 (SC UFH 360; SC LMWH 360) **Age (mean ± SD)**: SC UFH 65.7 ± 15.6 years; SC LMWH 67.0 ± 14.8 years **Sex M/F**: SC UFH 158/202; SC LMWH 167/193 **Inclusion criteria**: people with DVT of the lower extremities and/or PE were eligible for the study, provided that the suspicion was objectively confirmed **Exclusion criteria**: age less than 18 years, pregnancy, contraindications to anticoagulant treatment, full-dose anticoagulant treatment (either heparin or oral anticoagulants) for more than 24 h, haemodynamic instability, previous (less than 1 year earlier) episode of VTE, life expectancy less than 3 months, poor compliance, and geographic inaccessibility for follow-up **Diagnostic criteria**: a positive result of at least 1 of the following tests was accepted for inclusion: ascending phlebography, compression ultrasound of the proximal vein system, echo colour Doppler scan of the calf vein system in the case of clinical suspicion of DVT, ventilation-perfusion scanning, spiral computed tomographic scanning, and pulmonary angiography in the case of clinical suspicion of PE. In the presence of abnormal results of an ultrasound test of the lower extremities, the diagnosis of PE was also accepted if a perfusion lung scan was compatible with a high probability of PE when compared with the chest x-ray

Prandoni 2004 *(Continued)*

	Type of VTE: 601 DVT/119 PE
Interventions	**Intervention (route, total dose/day, frequency)**: IV bolus UFH (calcium heparin) 4000-5000 IU followed by SC UFH twice daily, aPTT adjusted + warfarin **Control (route, total dose/day, frequency)**: SC LMWH 85 U/kg twice daily + warfarin **Treatment before study**: NA
Outcomes	**Primary outcome**: recurrent VTE at 3 month follow-up **Secondary outcomes**: recurrent VTE during heparin treatment, bleeding during heparin treatment, death
Notes	**Stated aim of the study**: to assess the value of UFH or LMWH for treating the full spectrum of patients with VTE, including recurrent VTE and PE

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation … was performed with a computer algorithm"
Allocation concealment (selection bias)	Low risk	Use of a "24-hour telephone service that recorded patient information before disclosure of the treatment assigned"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Use of an open study design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used – no description of blinding outcome assessors Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – no description of blinding outcome assessors Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data used Minor bleeding: data used VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	Low risk	0 participants (out of 720) were withdrawn from the study "[N]o patients were lost to follow up" "We … ensured follow up was complete for all randomised patients"

Prandoni 2004 *(Continued)*

		During follow-up 24 participants died: In the UFH group 12 participants died (3 from PE and 1 from haemorrhage); in the LMWH group 12 participants died (4 from PE)
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other biases

Walker 1987

Methods	**Study design**: open randomised controlled trial **Duration of intervention**: 14 days **Duration of follow-up**: 14 days **Run-in period**: NA **Intention-to-treat analysis**: no **Language of publication**: English
Participants	**Who participated**: people with acute lower limb DVT **Country**: UK **Number of study centres**: 5 **Setting**: inpatients **Number**: 100 (SC UFH 50; IV continuous UFH 50) **Age (mean ± SD)**: SC UFH M 61 ± 11 years, F 63 ± 16 years; IV continuous UFH M 60 ± 14 years, F 63 ±15 years **Sex (M/F)**: SC UFH 25/25; IV continuous UFH 28/22 **Inclusion criteria**: people with DVT of the legs (calf + proximal), phlebography proven, with a thrombus > 5 cm **Exclusion criteria**: PE or occlusive thrombus **Diagnostic criteria**: phlebography
Interventions	**Intervention (route, total dose/day, frequency)**: SC UFH (calcium heparin) 250 U/kg, aPTT adjusted + warfarin **Control (route, total dose/day, frequency)**: IV continuous UFH (sodium heparin) aPTT adjusted + warfarin **Treatment before study**: NA
Outcomes	Outcomes not specified as primary or secondary **Outcomes**: DVT extension, injection site pain, PE, haemoglobin, platelets, aPTT
Notes	**Stated aim of the study**: to compare the efficacy and safety of SC versus IV heparin for leg DVT
Risk of bias	

Walker 1987 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"[T]he randomisation code was drafted using a standard random number table"
Allocation concealment (selection bias)	Low risk	"[P]atient allocations were taken from sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding provided Different methods of heparin administration – intravenous compared to subcutaneous – probably prevented adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Outcomes requiring blinding** Recurrent VTE at 3 months: data used – no description of blinding outcome assessors Recurrent DVT at 3 months: NA PE – excluding PE found at autopsy: data used – no description of blinding outcome assessors Incidence of heparin-induced thrombocytopenia: NA Incidence of asymptomatic recurrent VTE at 3 months: NA Quality of life: NA **Outcomes not requiring blinding** Major bleeding: data not used - not meeting ISTH definition Minor bleeding: data not used - not meeting definition of minor bleeding VTE-related mortality: data used All-cause mortality: data used
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants (out of 100) were withdrawn from the study, reasons for withdrawals are clearly presented: Intravenous group - 3 participants were excluded due to "technically unsatisfactory" phlebograms Subcutaneous group - 1 patient died during the course of the study
Selective reporting (reporting bias)	Low risk	The paper states that haemoglobin concentration; packed red cell count and platelet count were estimated on days 1,7,14 but no results are presented for these measurements. Nevertheless these were not outcomes of our review and therefore the study was judged to be at low risk of reporting bias
Other bias	Low risk	No evidence of other biases

aPTT: activated partial thromboplastin time;**AT**: antithrombin;**BP**: blood pressure; **DVT**: deep vein thrombosis;**INR**: international normalised ratio;**ISTH**: International Society on Thrombosis and Haemostasis; **IU**: international units; **IV**: intravenous; **LMWH**: low molecular weight heparin;**NA**: not applicable; **PE**: pulmonary embolism; **SC**: subcutaneous; **UFH**: unfractionated heparin;**US**: ultrasound; **VTE**: venous thromboembolism.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fagher 1981	RCT comparing continuous versus intermittent intravenous heparin administration in people diagnosed with DVT
Glazier 1976	RCT comparing continuous versus intermittent Intravenous heparin administration in people with PE
Gruber 1979	RCT comparing subcutaneous heparin and dextran for the prophylaxis of VTE
Horbach 1996	RCT comparing subcutaneous LMWH versus subcutaneous UFH for the prophylaxis of VTE
Lockner 1986	RCT comparing intravenous UFH versus intravenous LMWH in people diagnosed with DVT
Marchiori 2002	RCT of people diagnosed with superficial vein thrombosis
Monreal 1994	RCT comparing long-term treatment of people with VTE
Nakamura 2010	RCT comparing intravenous UFH versus LMWH in people diagnosed with PE
NCT01956955	RCT comparing UFH versus LMWH plus thrombolytic treatment in people diagnosed with PE
Quiros 2001	RCT comparing intravenous UFH versus intravenous LMWH in people diagnosed with DVT
Riess 2014	RCT comparing intravenous UFH versus LMWH in people diagnosed with PE
Rodgers 1999	RCT comparing intravenous UFH versus LMWH in people diagnosed with cancer-associated DVT
Romera 2009	RCT comparing LMWH versus VKA in people diagnosed with DVT
Ucar 2015	RCT comparing UFH versus LMWH plus thrombolytic treatment in people diagnosed with PE
Van Doormaal 2009	RCT comparing LMWH only in cancer-related VTE
Van Doormaal 2010	RCT comparing LMWH only in cancer-related DVT

DVT: deep vein thrombosis; **LMWH**: low molecular weight heparin; **PE**: pulmonary embolism; **RCT**: randomised controlled trial; **UFH**: unfractionated heparin; **VKA**: vitamin K antagonist; **VTE**: venous thromboembolism.

DATA AND ANALYSES

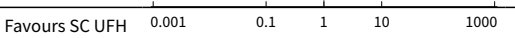
Comparison 1. Subcutaneous unfractionated heparin versus intravenous unfractionated heparin

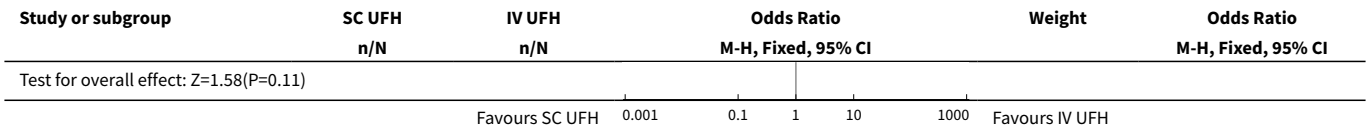
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic recurrent VTE at 3 months	8	965	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [0.89, 3.10]
1.1 DVT with/without PE	8	965	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [0.89, 3.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Symptomatic recurrent DVT at 3 months	1	115	Odds Ratio (M-H, Fixed, 95% CI)	3.29 [0.64, 17.06]
2.1 DVT with/without PE	1	115	Odds Ratio (M-H, Fixed, 95% CI)	3.29 [0.64, 17.06]
3 PE at 3 months	9	1161	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.73, 2.84]
3.1 DVT with/without PE	9	1161	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.73, 2.84]
4 VTE-related mortality at 3 months	9	1168	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.20, 4.88]
4.1 DVT with/without PE	9	1168	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.20, 4.88]
5 Major bleeding	4	583	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.42, 1.97]
5.1 DVT with/without PE	4	583	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.42, 1.97]
6 All-cause mortality	8	972	Odds Ratio (M-H, Fixed, 95% CI)	1.74 [0.67, 4.51]
6.1 DVT with/without PE	8	972	Odds Ratio (M-H, Fixed, 95% CI)	1.74 [0.67, 4.51]
7 Treatment related morbidity - minor bleeding	5	779	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.33, 1.20]
7.1 DVT with/without PE	5	779	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.33, 1.20]

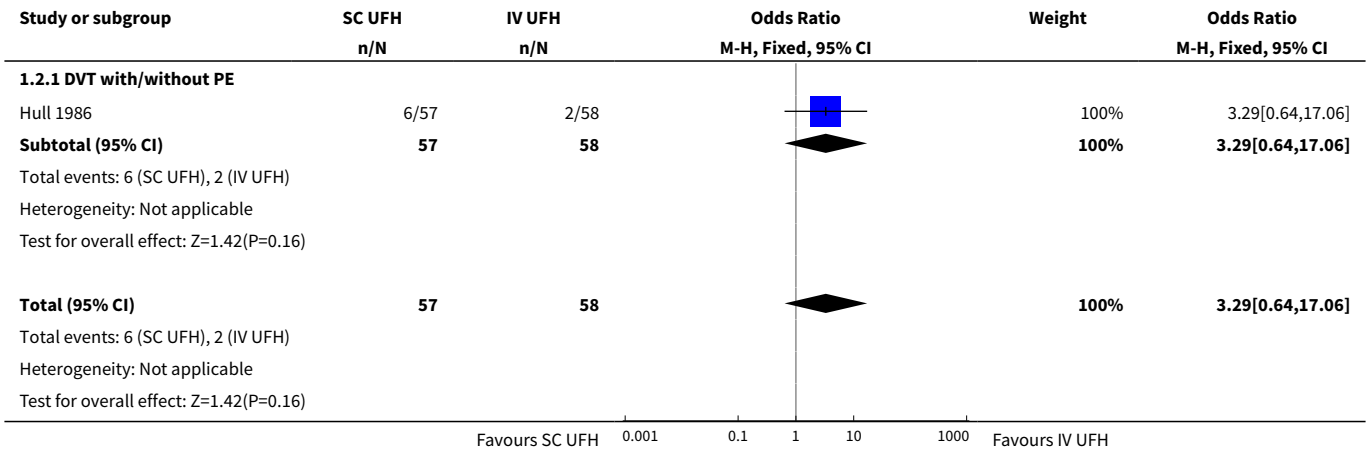
Analysis 1.1. Comparison 1 Subcutaneous unfractionated heparin versus intravenous unfractionated heparin, Outcome 1 Symptomatic recurrent VTE at 3 months.

Study or subgroup	SC UFH n/N	IV UFH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 DVT with/without PE					
Andersson 1982	1/72	1/69		6.49%	0.96[0.06,15.62]
Bentley 1980	1/50	1/50		6.32%	1[0.06,16.44]
Doyle 1987	5/47	5/49		28.2%	1.05[0.28,3.88]
Hull 1986	11/57	3/58		15.47%	4.38[1.15,16.66]
Krähenbühl 1979	1/23	1/25		5.91%	1.09[0.06,18.51]
Lopaciuk 1990	2/48	1/46		6.31%	1.96[0.17,22.34]
Pini 1990	4/138	2/133		12.75%	1.96[0.35,10.86]
Walker 1987	2/50	3/50		18.56%	0.65[0.1,4.09]
Subtotal (95% CI)	**485**	**480**		**100%**	**1.66[0.89,3.1]**
Total events: 27 (SC UFH), 17 (IV UFH)					
Heterogeneity: Tau^2=0; Chi^2=3.91, df=7(P=0.79); I^2=0%					
Test for overall effect: Z=1.58(P=0.11)					
Total (95% CI)	**485**	**480**		**100%**	**1.66[0.89,3.1]**
Total events: 27 (SC UFH), 17 (IV UFH)					
Heterogeneity: Tau^2=0; Chi^2=3.91, df=7(P=0.79); I^2=0%					

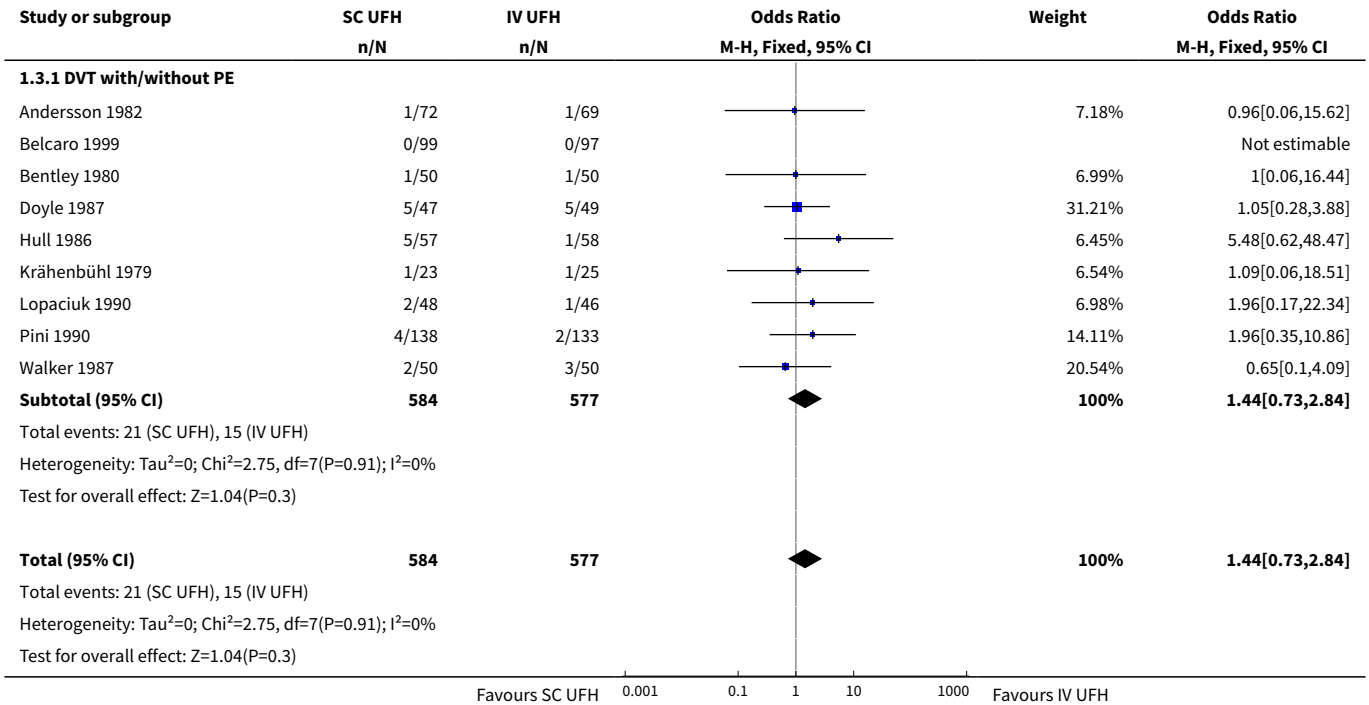




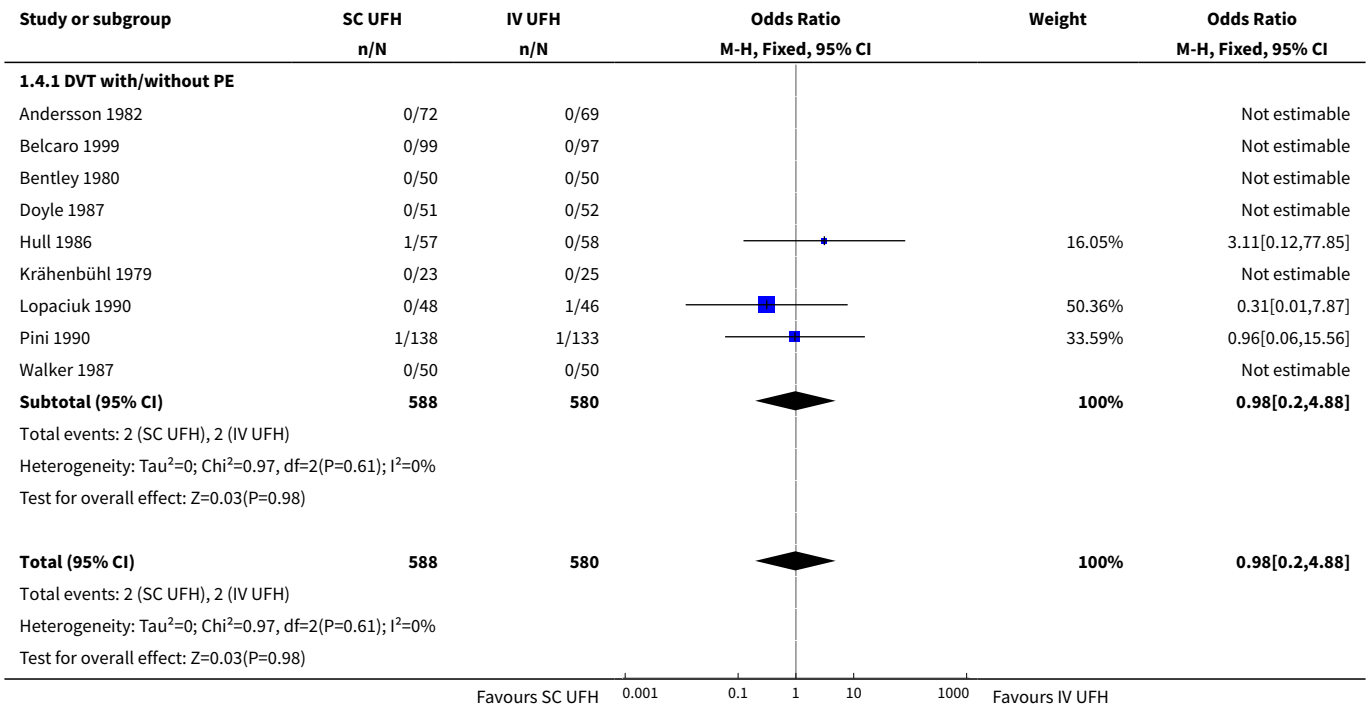
Analysis 1.2. Comparison 1 Subcutaneous unfractionated heparin versus intravenous unfractionated heparin, Outcome 2 Symptomatic recurrent DVT at 3 months.



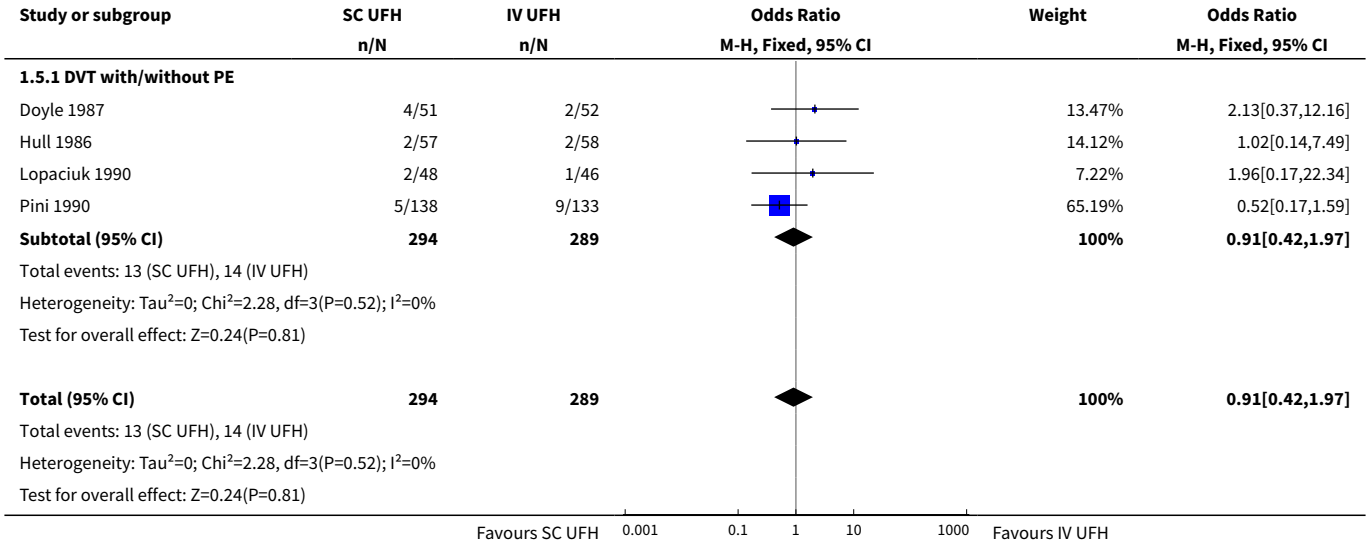
Analysis 1.3. Comparison 1 Subcutaneous unfractionated heparin versus intravenous unfractionated heparin, Outcome 3 PE at 3 months.



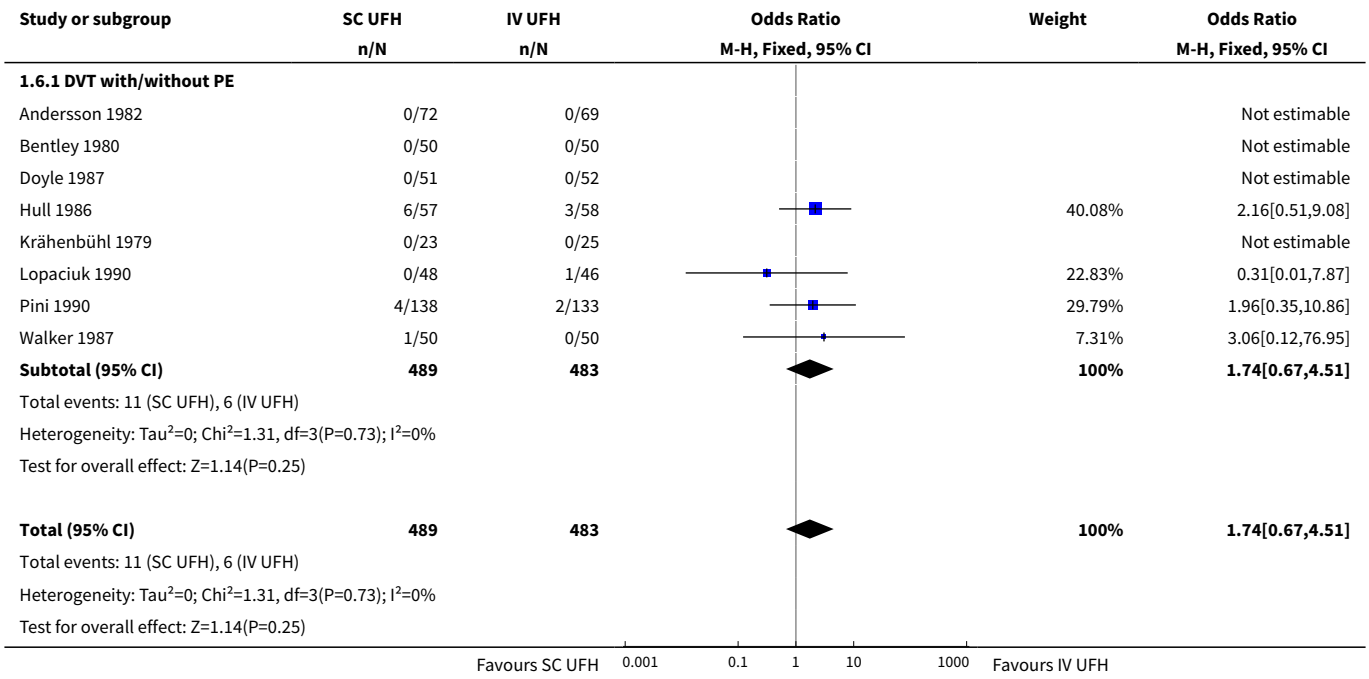
Analysis 1.4. Comparison 1 Subcutaneous unfractionated heparin versus intravenous unfractionated heparin, Outcome 4 VTE-related mortality at 3 months.



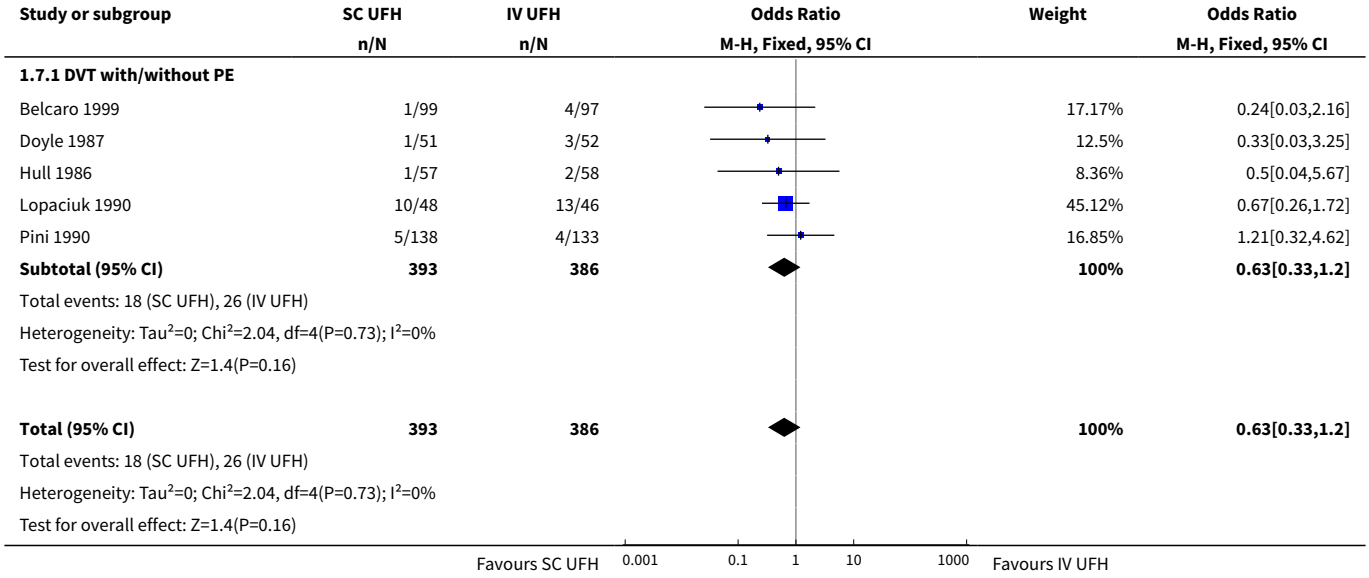
Analysis 1.5. Comparison 1 Subcutaneous unfractionated heparin versus intravenous unfractionated heparin, Outcome 5 Major bleeding.



Analysis 1.6. Comparison 1 Subcutaneous unfractionated heparin versus intravenous unfractionated heparin, Outcome 6 All-cause mortality.



Analysis 1.7. Comparison 1 Subcutaneous unfractionated heparin versus intravenous unfractionated heparin, Outcome 7 Treatment related morbidity - minor bleeding.

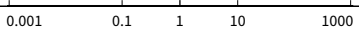


Comparison 2. Subcutaneous unfractionated heparin versus low molecular weight heparin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic recurrent VTE at 3 months	5	2156	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.63, 1.63]
1.1 DVT with/without PE	3	1954	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.57, 1.56]
1.2 DVT without PE	2	202	Odds Ratio (M-H, Fixed, 95% CI)	2.12 [0.38, 11.84]
2 Symptomatic recurrent DVT at 3 months	3	1566	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.73, 2.63]
2.1 DVT with/without PE	2	1420	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.65, 2.46]
2.2 DVT without PE	1	146	Odds Ratio (M-H, Fixed, 95% CI)	5.28 [0.25, 111.99]
3 PE at 3 months	5	1819	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.36, 1.96]
3.1 DVT with/without PE	2	1420	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.31, 2.04]
3.2 DVT without PE	3	399	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.14, 7.63]
4 VTE-related mortality at 3 months	8	2469	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.17, 1.67]
4.1 DVT with/without PE	4	2016	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.17, 1.67]
4.2 DVT without PE	4	453	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Major bleeding	5	2300	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.43, 1.20]
5.1 DVT with/without PE	3	1957	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.41, 1.16]
5.2 DVT without PE	2	343	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [0.13, 78.00]
6 All-cause mortality	7	2272	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.50, 1.07]
6.1 DVT with/without PE	4	2016	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.48, 1.05]
6.2 DVT without PE	3	256	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.22, 13.26]
7 Treatment related morbidity - minor bleeding	5	2300	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.71, 1.37]
7.1 DVT with/without PE	3	1957	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.43]
7.2 DVT without PE	2	343	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.44, 2.05]
8 Treatment related morbidity - HIT	3	1954	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [0.25, 9.14]
8.1 DVT with/without PE	3	1954	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [0.25, 9.14]

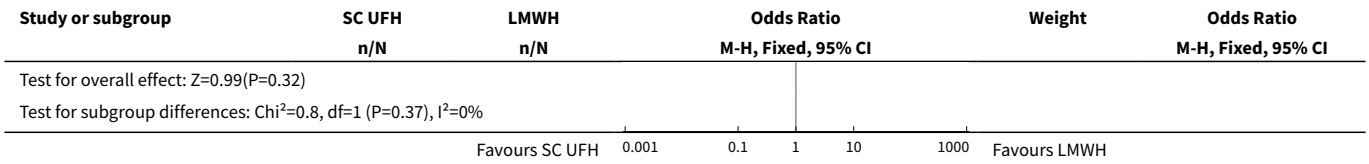
Analysis 2.1. Comparison 2 Subcutaneous unfractionated heparin versus low molecular weight heparin, Outcome 1 Symptomatic recurrent VTE at 3 months.

Study or subgroup	SC UFH n/N	LMWH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 DVT with/without PE					
Kearon 2006	13/348	12/352		34.15%	1.1[0.49,2.44]
Leizorovicz 2011	3/264	7/270		20.34%	0.43[0.11,1.69]
Prandoni 2004	15/360	14/360		39.89%	1.07[0.51,2.26]
Subtotal (95% CI)	**972**	**982**		**94.38%**	**0.95[0.57,1.56]**
Total events: 31 (SC UFH), 33 (LMWH)					
Heterogeneity: Tau^2=0; Chi^2=1.52, df=2(P=0.47); I^2=0%					
Test for overall effect: Z=0.22(P=0.82)					
2.1.2 DVT without PE					
Holm 1986	0/27	1/29		4.23%	0.35[0.01,8.85]
Lopaciuk 1992	3/72	0/74		1.4%	7.5[0.38,147.9]
Subtotal (95% CI)	**99**	**103**		**5.62%**	**2.12[0.38,11.84]**
Total events: 3 (SC UFH), 1 (LMWH)					
Heterogeneity: Tau^2=0; Chi^2=1.89, df=1(P=0.17); I^2=47.17%					
Test for overall effect: Z=0.86(P=0.39)					
Total (95% CI)	**1071**	**1085**		**100%**	**1.01[0.63,1.63]**
Total events: 34 (SC UFH), 34 (LMWH)					
Heterogeneity: Tau^2=0; Chi^2=3.72, df=4(P=0.44); I^2=0%					
Test for overall effect: Z=0.05(P=0.96)					
Test for subgroup differences: Chi^2=0.78, df=1 (P=0.38), I^2=0%					

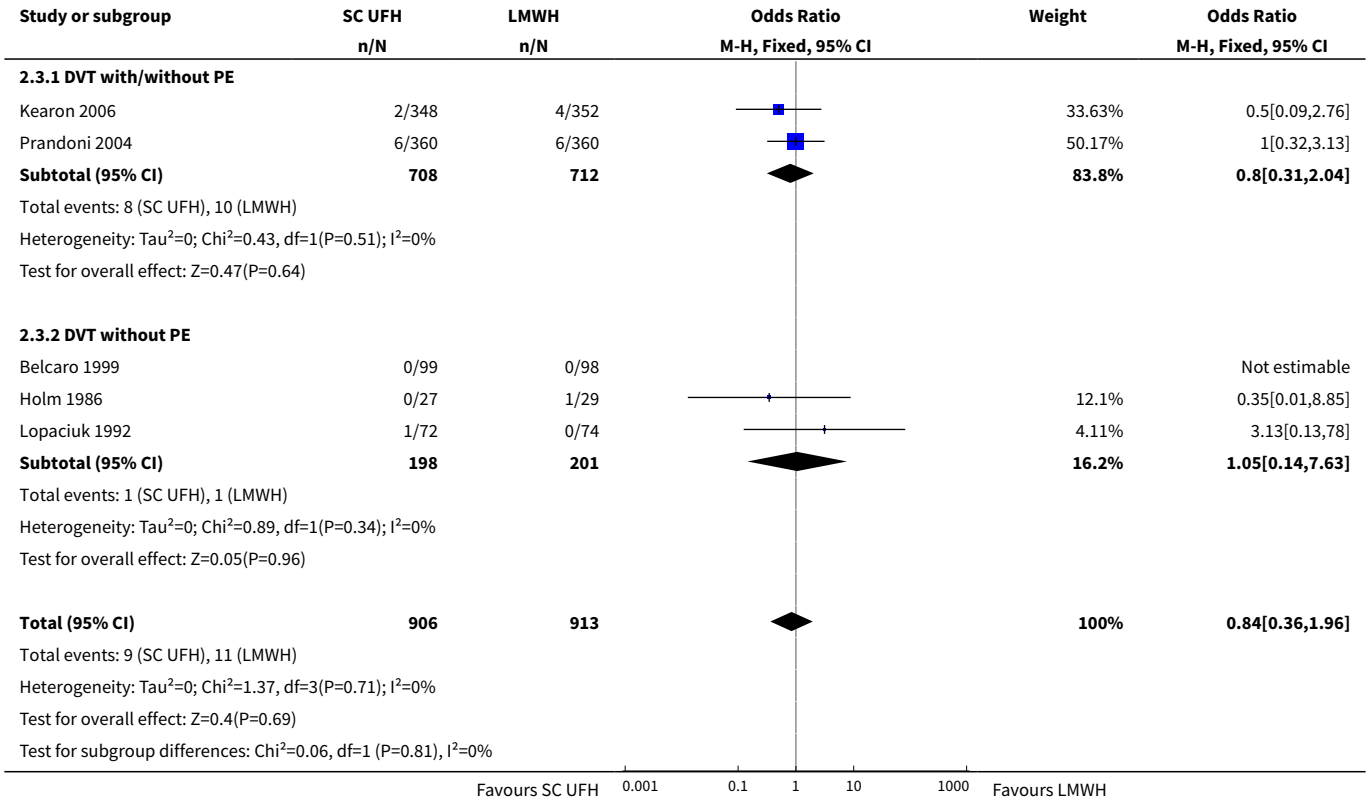


Analysis 2.2. Comparison 2 Subcutaneous unfractionated heparin versus low molecular weight heparin, Outcome 2 Symptomatic recurrent DVT at 3 months.

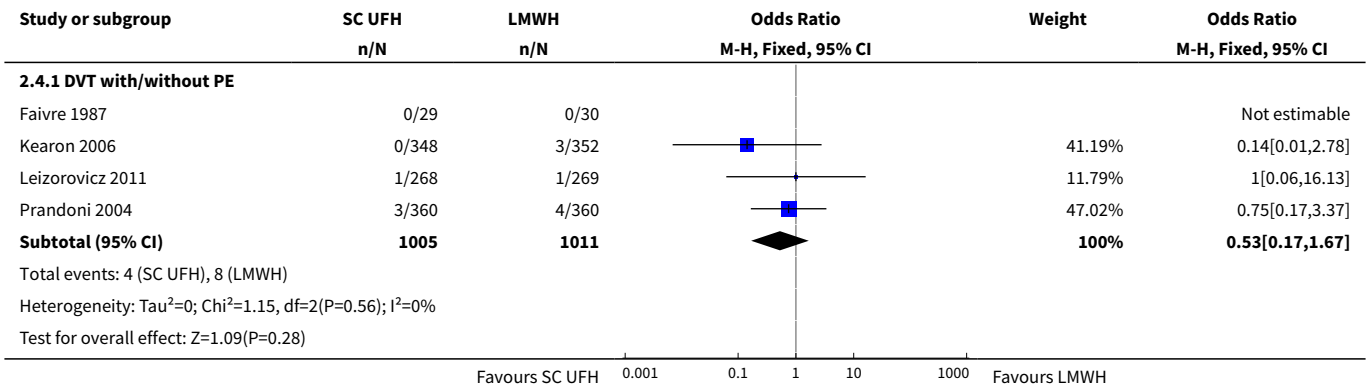
Study or subgroup	SC UFH n/N	LMWH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.2.1 DVT with/without PE					
Kearon 2006	11/348	8/352		48.21%	1.4[0.56,3.53]
Prandoni 2004	9/360	8/360		48.81%	1.13[0.43,2.96]
Subtotal (95% CI)	**708**	**712**		**97.02%**	**1.27[0.65,2.46]**
Total events: 20 (SC UFH), 16 (LMWH)					
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.75); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					
2.2.2 DVT without PE					
Lopaciuk 1992	2/72	0/74		2.98%	5.28[0.25,111.99]
Subtotal (95% CI)	**72**	**74**		**2.98%**	**5.28[0.25,111.99]**
Total events: 2 (SC UFH), 0 (LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.07(P=0.29)					
Total (95% CI)	**780**	**786**		**100%**	**1.38[0.73,2.63]**
Total events: 22 (SC UFH), 16 (LMWH)					
Heterogeneity: Tau^2=0; Chi^2=0.91, df=2(P=0.63); I^2=0%					

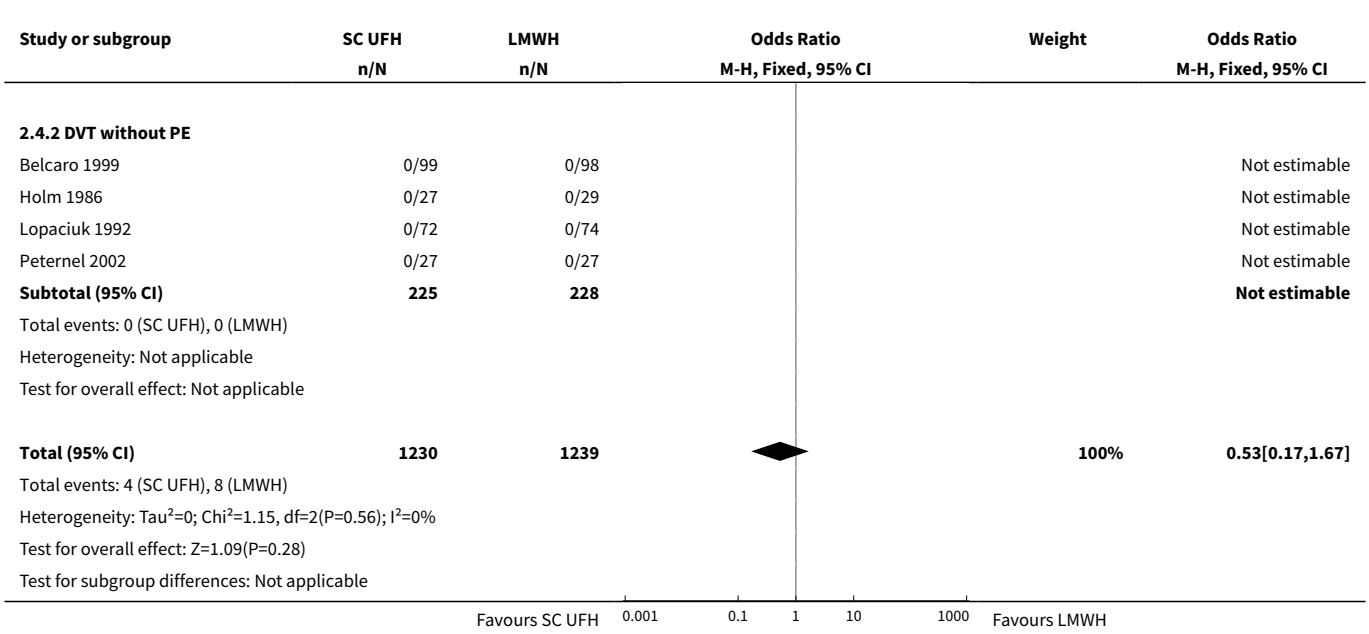


Analysis 2.3. Comparison 2 Subcutaneous unfractionated heparin versus low molecular weight heparin, Outcome 3 PE at 3 months.

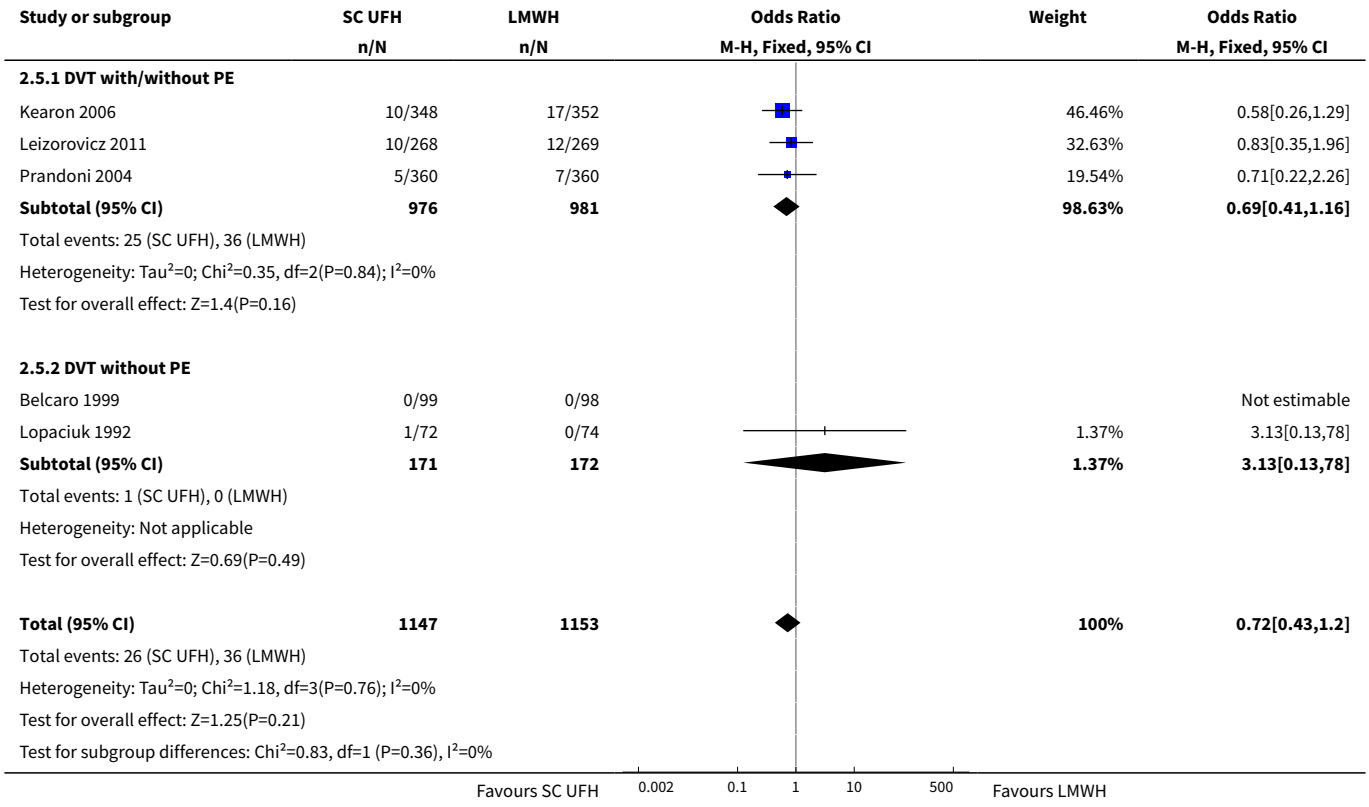


Analysis 2.4. Comparison 2 Subcutaneous unfractionated heparin versus low molecular weight heparin, Outcome 4 VTE-related mortality at 3 months.



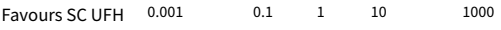


Analysis 2.5. Comparison 2 Subcutaneous unfractionated heparin versus low molecular weight heparin, Outcome 5 Major bleeding.



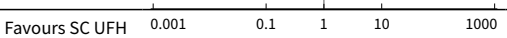
Analysis 2.6. Comparison 2 Subcutaneous unfractionated heparin versus low molecular weight heparin, Outcome 6 All-cause mortality.

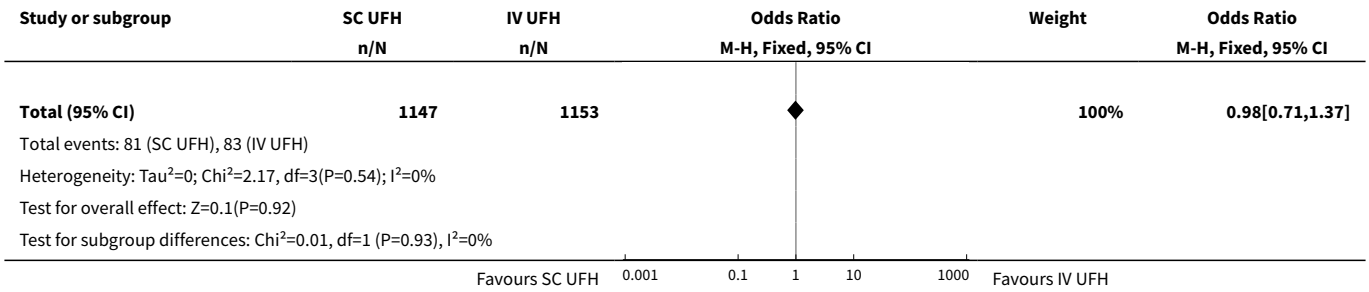
Study or subgroup	SC UFH n/N	LMWH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.6.1 DVT with/without PE					
Faivre 1987	0/29	0/30			Not estimable
Kearon 2006	18/348	22/352		33.05%	0.82[0.43,1.55]
Leizorovicz 2011	17/268	31/269		46.17%	0.52[0.28,0.96]
Prandoni 2004	12/360	12/360		18.48%	1[0.44,2.26]
Subtotal (95% CI)	**1005**	**1011**		**97.7%**	**0.71[0.48,1.05]**
Total events: 47 (SC UFH), 65 (LMWH)					
Heterogeneity: Tau²=0; Chi²=1.84, df=2(P=0.4); I²=0%					
Test for overall effect: Z=1.72(P=0.09)					
2.6.2 DVT without PE					
Holm 1986	0/27	0/29			Not estimable
Lopaciuk 1992	1/72	0/74		0.77%	3.13[0.13,78]
Peternel 2002	1/27	1/27		1.53%	1[0.06,16.85]
Subtotal (95% CI)	**126**	**130**		**2.3%**	**1.71[0.22,13.26]**
Total events: 2 (SC UFH), 1 (LMWH)					
Heterogeneity: Tau²=0; Chi²=0.27, df=1(P=0.6); I²=0%					
Test for overall effect: Z=0.51(P=0.61)					
Total (95% CI)	**1131**	**1141**		**100%**	**0.73[0.5,1.07]**
Total events: 49 (SC UFH), 66 (LMWH)					
Heterogeneity: Tau²=0; Chi²=2.69, df=4(P=0.61); I²=0%					
Test for overall effect: Z=1.59(P=0.11)					
Test for subgroup differences: Chi²=0.68, df=1 (P=0.41), I²=0%					



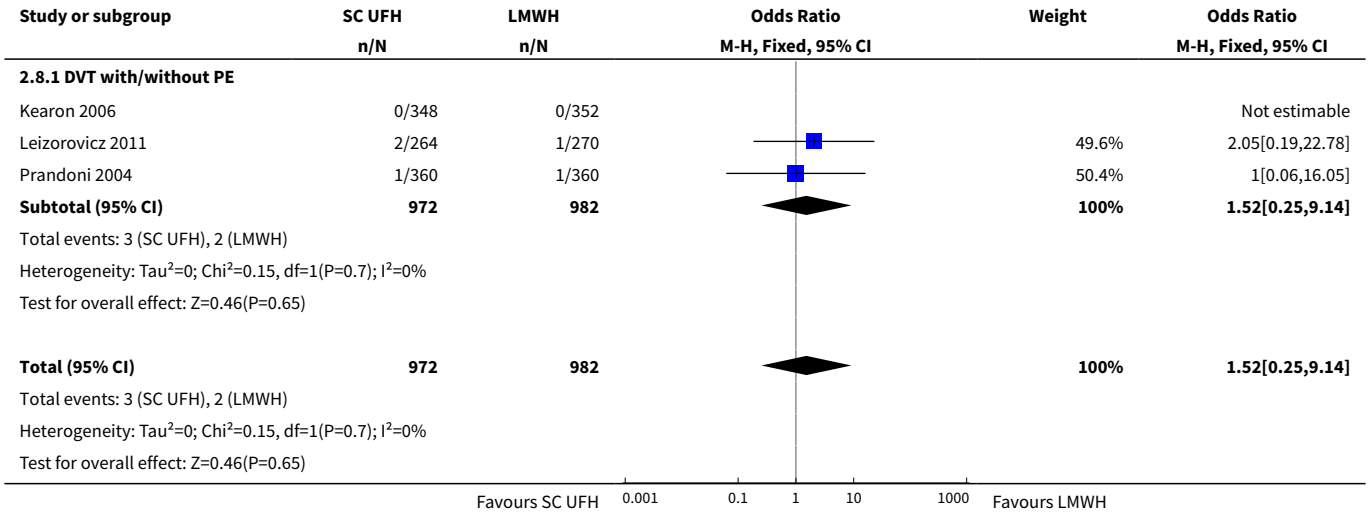
Analysis 2.7. Comparison 2 Subcutaneous unfractionated heparin versus low molecular weight heparin, Outcome 7 Treatment related morbidity - minor bleeding.

Study or subgroup	SC UFH n/N	IV UFH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.7.1 DVT with/without PE					
Kearon 2006	23/348	18/352		23.51%	1.31[0.7,2.48]
Leizorovicz 2011	43/268	49/269		57.76%	0.86[0.55,1.35]
Prandoni 2004	0/360	0/360			Not estimable
Subtotal (95% CI)	**976**	**981**		**81.27%**	**0.99[0.69,1.43]**
Total events: 66 (SC UFH), 67 (IV UFH)					
Heterogeneity: Tau²=0; Chi²=1.15, df=1(P=0.28); I²=12.88%					
Test for overall effect: Z=0.06(P=0.96)					
2.7.2 DVT without PE					
Belcaro 1999	1/99	3/98		4.2%	0.32[0.03,3.16]
Lopaciuk 1992	14/72	13/74		14.53%	1.13[0.49,2.61]
Subtotal (95% CI)	**171**	**172**		**18.73%**	**0.95[0.44,2.05]**
Total events: 15 (SC UFH), 16 (IV UFH)					
Heterogeneity: Tau²=0; Chi²=1.03, df=1(P=0.31); I²=2.76%					
Test for overall effect: Z=0.13(P=0.9)					





Analysis 2.8. Comparison 2 Subcutaneous unfractionated heparin versus low molecular weight heparin, Outcome 8 Treatment related morbidity - HIT.



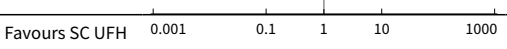
Comparison 3. Subcutaneous unfractionated heparin versus low molecular weight heparin (excluding large studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic recurrent VTE at 3 months	3	736	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.29, 2.16]
2 Symptomatic recurrent DVT at 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 PE at 3 months	3	399	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.14, 7.63]
4 VTE-related mortality at 3 months	6	1049	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 16.13]
5 Major bleeding	3	880	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.41, 2.09]
6 All-cause mortality	5	852	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.32, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Treatment-related morbidity	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Minor bleeding	3	880	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.60, 1.30]
7.2 Heparin-induced thrombocytopenia	1	534	Odds Ratio (M-H, Fixed, 95% CI)	2.05 [0.19, 22.78]

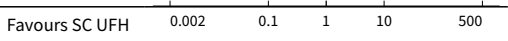
Analysis 3.1. Comparison 3 Subcutaneous unfractionated heparin versus low molecular weight heparin (excluding large studies), Outcome 1 Symptomatic recurrent VTE at 3 months.

Study or subgroup	SC UFH n/N	LMWH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Holm 1986	0/27	1/29		16.28%	0.35[0.01,8.85]
Leizorovicz 2011	3/264	7/270		78.34%	0.43[0.11,1.69]
Lopaciuk 1992	3/72	0/74		5.38%	7.5[0.38,147.9]
Total (95% CI)	**363**	**373**		**100%**	**0.8[0.29,2.16]**
Total events: 6 (SC UFH), 8 (LMWH)					
Heterogeneity: Tau^2=0; Chi^2=3.21, df=2(P=0.2); I^2=37.62%					
Test for overall effect: Z=0.44(P=0.66)					



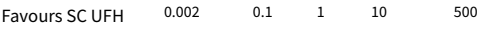
Analysis 3.2. Comparison 3 Subcutaneous unfractionated heparin versus low molecular weight heparin (excluding large studies), Outcome 2 Symptomatic recurrent DVT at 3 months.

Study or subgroup	SC UFH n/N	LMWH n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lopaciuk 1992	2/72	0/74		5.28[0.25,111.99]



Analysis 3.3. Comparison 3 Subcutaneous unfractionated heparin versus low molecular weight heparin (excluding large studies), Outcome 3 PE at 3 months.

Study or subgroup	SC UFH n/N	LMWH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Belcaro 1999	0/99	0/98			Not estimable
Holm 1986	0/27	1/29		74.65%	0.35[0.01,8.85]
Lopaciuk 1992	1/72	0/74		25.35%	3.13[0.13,78]
Total (95% CI)	**198**	**201**		**100%**	**1.05[0.14,7.63]**
Total events: 1 (SC UFH), 1 (LMWH)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=0.05(P=0.96)					



Analysis 3.4. Comparison 3 Subcutaneous unfractionated heparin versus low molecular weight heparin (excluding large studies), Outcome 4 VTE-related mortality at 3 months.

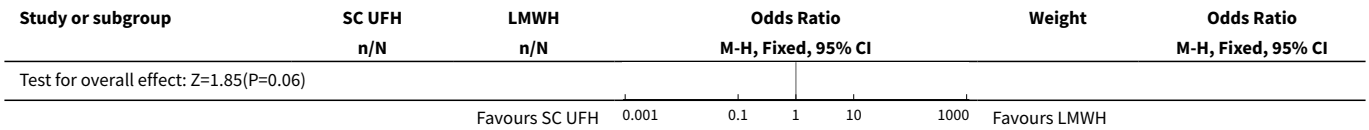
Study or subgroup	SC UFH n/N	LMWH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Belcaro 1999	0/99	0/98			Not estimable
Faivre 1987	0/29	0/30			Not estimable
Holm 1986	0/27	0/29			Not estimable
Leizorovicz 2011	1/268	1/269		100%	1[0.06,16.13]
Lopaciuk 1992	0/72	0/74			Not estimable
Peternel 2002	0/27	0/27			Not estimable
Total (95% CI)	**522**	**527**		**100%**	**1[0.06,16.13]**
Total events: 1 (SC UFH), 1 (LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0(P=1)					

Analysis 3.5. Comparison 3 Subcutaneous unfractionated heparin versus low molecular weight heparin (excluding large studies), Outcome 5 Major bleeding.

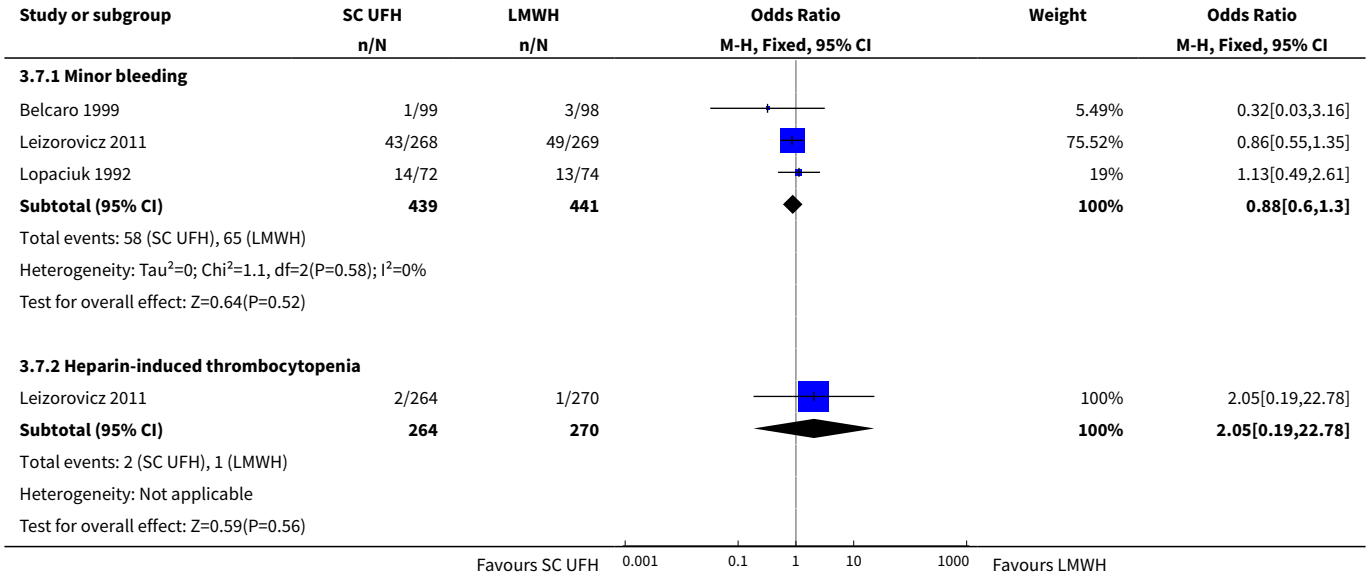
Study or subgroup	SC UFH n/N	LMWH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Belcaro 1999	0/99	0/98			Not estimable
Leizorovicz 2011	10/268	12/269		95.98%	0.83[0.35,1.96]
Lopaciuk 1992	1/72	0/74		4.02%	3.13[0.13,78]
Total (95% CI)	**439**	**441**		**100%**	**0.92[0.41,2.09]**
Total events: 11 (SC UFH), 12 (LMWH)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=0.19(P=0.85)					

Analysis 3.6. Comparison 3 Subcutaneous unfractionated heparin versus low molecular weight heparin (excluding large studies), Outcome 6 All-cause mortality.

Study or subgroup	SC UFH n/N	LMWH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Faivre 1987	0/29	0/30			Not estimable
Holm 1986	0/27	0/29			Not estimable
Leizorovicz 2011	17/268	31/269		95.25%	0.52[0.28,0.96]
Lopaciuk 1992	1/72	0/74		1.59%	3.13[0.13,78]
Peternel 2002	1/27	1/27		3.16%	1[0.06,16.85]
Total (95% CI)	**423**	**429**		**100%**	**0.58[0.32,1.03]**
Total events: 19 (SC UFH), 32 (LMWH)					
Heterogeneity: Tau^2=0; Chi^2=1.31, df=2(P=0.52); I^2=0%					



Analysis 3.7. Comparison 3 Subcutaneous unfractionated heparin versus low molecular weight heparin (excluding large studies), Outcome 7 Treatment-related morbidity.



APPENDICES

Appendix 1. CENTRAL search strategy

#1	MESH DESCRIPTOR Thrombosis	1238
#2	MESH DESCRIPTOR Thromboembolism	899
#3	MESH DESCRIPTOR Venous Thromboembolism	242
#4	MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES	2005
#5	(thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboembol* or thrombos* or embol* or microembol*):TI,AB,KY	17662
#6	MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES	735
#7	(PE or DVT or VTE):TI,AB,KY	4611
#8	((vein* or ven*) near thromb*):TI,AB,KY	6276

(Continued)

#9	(blood near3 clot*):TI,AB,KY	2696
#10	(pulmonary near3 clot*):TI,AB,KY	5
#11	(lung near3 clot*):TI,AB,KY	4
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	22923
#13	MESH DESCRIPTOR Heparin	2794
#14	(unfractionated or UFH):TI,AB,KY	1235
#15	*heparin*:TI,AB,KY	8806
#16	(calciparin* or eparin* or liquaemin or panheprin or multiparin* or hepalean or CY216):TI,AB,KY	39
#17	heparinic:TI,AB,KY	1
#18	#13 OR #14 OR #15 OR #16 OR #17	8855
#19	#12 AND #18	4164

Appendix 2. Trial registries searches

Clinicaltrials.gov

97 studies for (thrombosis OR embolism) AND heparin AND randomized AND (subcutaneous OR sc OR s.c)

WHO

32 records for 9 trials found

subcutaneous OR sc OR s.c in title

and

thrombosis OR embolism in condition

and

heparin in intervention

ISRCTN

No results found for Condition: thrombosis OR embolism AND Interventions: heparin AND subcutaneous

Appendix 3. Additional study information

Study ID	Setting (in or out patient) of SC administration	Control	Initial IV heparin bolus before SC administration?	Vitamin K antagonist	Vitamin K antagonist timing	Dose adjustment
Andersson 1982	Inpatient	IV heparin	Yes	Warfarin	1-2 days	aPTT

(Continued)

Belcaro 1999	Inpatient and outpatient	IV heparin + LMWH	No	No (SC extended period)	NA	Fixed dose
Bentley 1980	Inpatient	IV heparin	No	Warfarin	3 days	aPTT
Doyle 1987	Inpatient	IV heparin	Yes	Warfarin	7 days	aPTT
Faivre 1987	Inpatient	LMWH	No	Not stated	NA	aPTT
Holm 1986	Inpatient	LMWH	Yes (first 24 hours continuous)	Warfarin	1 day	Anti Xa inhibitor
Hull 1986	Inpatient	IV heparin	Yes	Warfarin	6-7 days	aPTT
Kearon 2006	Inpatient and outpatient	LMWH	No	Warfarin	1 day	Weight adjusted
Krähenbühl 1979	Inpatient	IV heparin	Yes	Unclear	NA	aPTT
Leizorovicz 2011	Inpatient	LMWH	Unclear	Unclear	1-3 days	aPTT
Lopaciuk 1990	Inpatient	IV heparin	Yes	Sintron	Unclear	aPTT
Lopaciuk 1992	Inpatient	LMWH	Yes	Sintron	7 days	aPTT
Peternel 2002	Inpatient	LMWH	Yes	Warfarin	2 days	aPTT
Pini 1990	Inpatient	IV heparin	No	Sintron	3 days	Unclear
Prandoni 2004	Inpatient	LMWH	Yes	Warfarin	2 days	aPTT
Walker 1987	Inpatient	IV heparin	No	Warfarin	7 days	aPTT

aPTT: activated partial thromboplastin time; **IV**: intravenous; **LMWH**: low molecular weight heparin; **NA**: not applicable; **SC**: subcutaneous.

WHAT'S NEW

Date	Event	Description
9 November 2018	Review declared as stable	This Cochrane review has been marked stable and will only be updated should new studies be identified.

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 4, 2009

Date	Event	Description
30 November 2016	New search has been performed	Searches rerun. One new study included and nine new studies excluded.
30 November 2016	New citation required but conclusions have not changed	Searches rerun. One new study included and nine new studies excluded. Review updated using current Cochrane standards. New authors have taken over this review.

CONTRIBUTIONS OF AUTHORS

JS: selected and assessed the quality of trials for inclusion in this update, extracted and entered data for analyses, and wrote the text of the review.
LR: selected and assessed the quality of trials for inclusion in this update, extracted and entered data for analyses, and wrote the text of the review.

DECLARATIONS OF INTEREST

JS: none known.
LR: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

  The Cochrane Vascular editorial base is supported by the Chief Scientist Office.
- National Institute for Health Research (NIHR), UK.

  This project was supported by the NIHR, via Cochrane Programme Grant funding Cochrane Vascular (13/89/23). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update, we amended the outcomes of the review to reflect current terminology and practice. We redefined the outcome 'treatment-related serious adverse effects, i.e. major bleeding; overall mortality' as two events, namely 'all-cause mortality' and 'major bleeding'. In addition, we used a more comprehensive definition of bleeding.

NOTES

This Cochrane review has been marked stable and will only be updated if new studies are identified as people are moving towards LMWH and newer drugs in favour of UFH.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anticoagulants [*administration & dosage] [adverse effects]; Heparin [*administration & dosage] [adverse effects]; Heparin, Low-Molecular-Weight [administration & dosage] [adverse effects]; Infusions, Intravenous; Injections, Subcutaneous; Randomized Controlled Trials as Topic; Recurrence; Venous Thromboembolism [*drug therapy]; Venous Thrombosis [drug therapy]

MeSH check words

Humans