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Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction) (Review)

Alikhan R, Forster R, Cohen AT

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Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction) (Review)

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[Intervention Review]

Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction)

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raza@doctors.org.uk.**Editorial group:** Cochrane Vascular Group.**Publication status and date:** Edited (no change to conclusions), comment added to review, published in Issue 2, 2018.**Citation:** Alikhan R, Forster R, Cohen AT. Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction). *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD003747. DOI: [10.1002/14651858.CD003747.pub4](https://doi.org/10.1002/14651858.CD003747.pub4).

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ABSTRACT

Background

Venous thromboembolic disease has been extensively studied in surgical patients. The benefit of thromboprophylaxis is now generally accepted, but it is medical patients who make up the greater proportion of the hospital population. Medical patients differ from surgical patients with regard to their health and the pathogenesis of thromboembolism and the impact that preventative measures can have. The extensive experience from thromboprophylaxis studies in surgical patients is therefore not necessarily applicable to non-surgical patients. This is an update of a review first published in 2009.

Objectives

To determine the effectiveness and safety of heparin (unfractionated heparin or low molecular weight heparin) thromboprophylaxis in acutely ill medical patients admitted to hospital, excluding those admitted to hospital with an acute myocardial infarction or stroke (ischaemic or haemorrhagic) or those requiring admission to an intensive care unit (unless the study population can be clearly defined as acute medical and not post-surgical).

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched November 2013) and CENTRAL (2013, Issue 10).

Selection criteria

Randomised controlled trials comparing unfractionated heparin (UFH) or low molecular weight heparin (LMWH) with placebo or no treatment, or comparing UFH with LMWH.

Data collection and analysis

One review author identified possible trials and a second review author confirmed their eligibility for inclusion in the review. Two review authors extracted the data. Disagreements were resolved by discussion. We performed the meta-analysis using a fixed-effect model with the results expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Main results

Sixteen studies with a combined total of 34,369 participants with an acute medical illness were included in this review. We identified 10 studies comparing heparin with placebo or no treatment and six studies comparing LMWH to UFH. Just under half of the studies had an

open-label design, putting them at a risk of performance bias. Descriptions of random sequence generation and allocation concealment were missing in most of the studies. Heparin reduced the odds of deep vein thrombosis (DVT) (OR 0.41, 95% CI 0.25 to 0.67; $P = 0.0004$). The estimated reductions in symptomatic non-fatal pulmonary embolism (PE) (OR 0.46; 95% CI 0.20 to 1.07; $P = 0.07$), fatal PE (OR 0.71; 95% CI 0.43 to 1.15; $P = 0.16$) and in combined non-fatal PE and fatal PE (OR 0.66, 95% CI 0.43 to 1.02; $P = 0.06$) associated with heparin were imprecise. Heparin resulted in an increase in major haemorrhage (OR 1.65, 95% CI 1.01 to 2.71; $P = 0.05$). There was no clear evidence that heparin had an effect on all-cause mortality and thrombocytopenia. Compared with UFH, LMWH reduced the risk of DVT (OR 0.77; 95% CI 0.62 to 0.96; $P = 0.02$) and major bleeding (OR 0.43; 95% CI 0.22 to 0.83; $P = 0.01$). There was no clear evidence that the effects of LMWH and UFH differed for the PE outcomes, all-cause mortality and thrombocytopenia.

Authors' conclusions

The data from this review describe a reduction in the risk of DVT in patients presenting with an acute medical illness who receive heparin thromboprophylaxis. This needs to be balanced against an increase in the risk of bleeding associated with thromboprophylaxis. The analysis favoured LMWH compared with UFH, with a reduced risk of both DVT and bleeding.

PLAIN LANGUAGE SUMMARY

Heparin to prevent deep vein thrombosis or pulmonary embolism in acutely ill medical patients (excluding those with stroke or myocardial infarction)

Blood clots may form in the veins of patients who are admitted to hospital suffering from an acute medical illness. These types of blood clots are referred to as deep vein thromboses (DVT) and they may break free from the blood vessel wall and travel to the lungs and cause death, at which point they are referred to as a pulmonary embolism (PE). These types of blood clots and their prevention have been thoroughly studied in surgical patients but not as much in non-surgical, medical patients, who make up a greater proportion of hospital patients. Medical patients differ from surgical patients with regard to their health, the progression of clots and the impact that preventative measures can have. The extensive experience from clot prevention studies in surgical patients is therefore not necessarily applicable to non-surgical patients.

Heparin is a blood thinning drug, which has been shown to reduce the occurrence of blood clots in patients after they have had surgery. Heparin exists in two forms, the original unfractionated (UFH) form and a newer form called low molecular weight heparin (LMWH). The aim of the current review is to determine the effectiveness and safety of heparin (UFH or LMWH) to prevent DVTs and PEs in non-surgical, medical patients admitted to hospital, excluding those admitted to hospital with a heart attack or stroke or those requiring admission to an intensive care unit. The outcomes investigated in this review were DVT, PE that did not cause death, PE that resulted in death, combined non-fatal and fatal PE, all-cause death, bleeding complications and thrombocytopenia, which is a condition that can be caused by heparin and results in decreased platelets in the blood.

This review of 16 trials in 34,369 non-surgical patients who suffered an acute medical illness found that heparin reduced the number of patients suffering DVTs but also increased the risk of bleeding complications when compared to participants that received a placebo or no medication. We had some concerns over how reliable the results were from the unblinded studies, which made up just under half of the studies. Also, most of the studies were lacking explanations of how the allocation of the treatments was performed. The lower risk of PEs (when combining those that caused death and those that did not) with heparin could have been a chance effect. There was no clear evidence of a difference in the rate of death or thrombocytopenia. The review also found that patients who were given LMWH developed fewer DVTs and fewer bleeding complications compared with those given UFH, leading to the conclusion that LMWH is more effective and carries a lower risk of adverse events in preventing blood clots than with UFH. There was no clear evidence of differences between LMWH and UFH for PE, death or thrombocytopenia.

BACKGROUND

Description of the condition

Venous thromboembolism (VTE) is a major health problem, the significance and seriousness of which is often not fully appreciated. VTE is one of the most important preventable causes of morbidity and mortality in hospital patients, having an annual incidence of one per 1000 individuals (Dahlback 2008). Most clinicians, whatever their specialty, will experience patients with this condition.

Description of the intervention

During the past 40 years numerous studies have shown that UFH and LMWH are effective and safe for the prevention of VTE in surgical patients (Geerts 2008). This has led to the widespread use of these agents for thromboprophylaxis in surgical patients with a resultant reduction in the incidence of fatal PE (Cohen 1996). During the same period of time, there have been fewer trials investigating the benefits and risks of thromboprophylaxis in medical patients. Most of these studies have concentrated on specific conditions such as myocardial infarction (MI) (Collins 1996) and ischaemic stroke (Gubitz 2004).

How the intervention might work

Thrombosis results from a disturbance in the balance between pro-thrombotic and antithrombotic forces that exist within the blood stream. The pro-thrombotic forces include platelets and the formation of fibrin. There are two phases of normal haemostasis; the first phase is platelet activation and adhesion, and the forming of a 'platelet plug'. In parallel, the second phase results in the activation of a series of procoagulant clotting factors, which generate a burst of thrombin, formation of fibrin and stabilisation of the platelet plug, resulting in a thrombus. When this process becomes unregulated venous thrombosis may occur in any vein in the body, although it usually occurs in the deep veins of the lower limbs. People admitted to hospital with an acute medical illness appear to be particularly at risk of suffering from thrombosis of these lower limb deep veins.

Heparin (UFH and LMWH) binds to a naturally occurring anticoagulant, antithrombin (AT), via a pentasaccharide sequence. The heparin-AT complex inactivates thrombin (factor IIa) as well as coagulation factors Xa, IXa and XIa. As a direct result of inactivating or reducing the generation of thrombin, fibrin formation is inhibited, as is thrombin directed activation of coagulation factors V, VIII and XI. In addition, thrombin mediated platelet activation is attenuated (Garcia 2012). Therefore, heparin affects both the primary and secondary phases of thrombus formation and this is the rationale behind its use as a thromboprophylactic agent.

Why it is important to do this review

Unlike their surgical counterparts, it wasn't until the late 1990s and early part of the 21st century that physicians caring for general medical patients had convincing evidence of the efficacy and safety of thromboprophylaxis for their patients upon which to base prescribing decisions (Geerts 2008). We believe that this has resulted in the underuse of thromboprophylaxis in the medical setting (Alikhan 2001), and this continues to be a problem (Cohen 2008). The under use may in part explain the high incidence rate of fatal PE in this patient group (Alikhan 2004; Sandler 1989). This is an update of a review first published in 2009 (Alikhan 2009).

OBJECTIVES

The aim of this review is to determine the effectiveness and safety of heparin (unfractionated heparin (UFH) or low molecular weight heparin (LMWH)) thromboprophylaxis in acutely ill medical patients admitted to hospital, excluding those admitted to hospital with an acute myocardial infarction or stroke (ischaemic or haemorrhagic) or those requiring admission to an intensive care unit (unless the study population can be clearly defined as acute medical and not post-surgical).

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomised controlled trials comparing UFH with placebo or no treatment
2. Randomised controlled trials comparing LMWH with placebo or no treatment
3. Randomised controlled trials comparing UFH with LMWH

Types of participants

People over the age of 18 years admitted to hospital with an acute medical illness, for example:

- heart failure;
- respiratory failure;
- cancer*;
- acute infection;
- episode of inflammatory bowel disease;
- acute rheumatic disorder.

*Studies that primarily involve cancer patients not in an acute medical setting are excluded, such as receiving chemotherapy in tandem with thromboprophylaxis. This is the subject of another Cochrane review (Di Nisio 2012).

Studies involving participants with only myocardial infarction or stroke are excluded because the risk of VTE differs in this population, and therefore the need for thromboprophylaxis. Collins 1996 and Geerts 2001 address these patient populations in reference to VTE and thromboprophylaxis.

We included studies from intensive care units if they clearly defined their population as medical and not post-surgical. Studies were excluded if they did not clearly define their intensive care unit population as suffering from acute medical illness.

Types of interventions

Participants randomised to receive UFH, LMWH, placebo or no treatment. Fondaparinux and other pentasaccharide agents were excluded from this review as they are addressed in another Cochrane review that is currently in progress (Song 2011).

Types of outcome measures

Primary outcomes

Efficacy

- Asymptomatic or symptomatic deep vein thrombosis (DVT) of the lower limbs detected by fibrinogen uptake test, ultrasound, venography or plethysmography
- Symptomatic non-fatal PE detected by ventilation perfusion scan, computed tomography, pulmonary angiography, or confirmed at autopsy

Safety

- Major haemorrhage. As it was not possible to obtain a standardised definition of major bleeding, the study author's definition, where given, was used. See [Characteristics of included studies](#) for individual study definitions

Secondary outcomes

Efficacy

- All-cause mortality
- Fatal PE
- Combined clinically symptomatic non-fatal PE and fatal PE

Safety

- Minor haemorrhage. As it was not possible to obtain a standardised definition of minor bleeding, the study author's definition, where given, was used. See [Characteristics of included studies](#) for individual study definitions
- Thrombocytopenia, as defined by individual study authors

Search methods for identification of studies

There was no restriction on the language of publication.

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched November 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 10), part of *The Cochrane Library* (www.thecochranelibrary.com). See [Appendix 1](#) for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL and AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the [Specialised Register](#) section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

Searching other resources

In the previous version of this review we consulted with colleagues and investigators as well as the manufacturers of the various LMWH preparations to identify unpublished or missed studies. This was not done for the current version.

Data collection and analysis

Selection of studies

For this update one review author (RA) identified possible trials, and the trial reports were assessed independently by another review author (RB) to confirm eligibility for inclusion in the review. In the previous version of this review study selection was performed by RA and AC.

Data extraction and management

For this update, RA and RB individually extracted the data using the following endpoints: DVT of the lower limbs; symptomatic non-fatal PE; fatal PE; combined symptomatic non-fatal and fatal PE; all-cause mortality; major and minor bleeding (as defined by individual authors); and thrombocytopenia (reduced numbers of platelets). We recorded all information collected on data extraction forms. We resolved disagreements by discussion. In the previous version of this review data extraction was performed by RA and AC.

Assessment of risk of bias in included studies

The methodological quality of included trials was assessed independently by RA and RB using the 'Risk of bias' tool from The Cochrane Collaboration ([Higgins 2011](#)). The following domains were assessed: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel, and blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. The domains were classified as low risk of bias, high risk of bias, or unclear risk of bias according to the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Disagreements were resolved by discussion between the two review authors assessing bias.

Measures of treatment effect

We performed statistical analyses according to the statistical guidelines for authors recommended by the Cochrane Peripheral Vascular Diseases Group.

We divided the studies into two groups and analysed them separately:

1. heparin (UFH or LMWH) prophylaxis versus placebo or no treatment;
2. LMWH versus UFH.

For each of the two groups we pooled data from each study on DVT, non-fatal PE, fatal PE, combined non-fatal and fatal PE, all-cause mortality, major bleeding, minor bleeding, and thrombocytopenia in order to arrive at an overall estimate of efficacy and safety of heparin versus no treatment or placebo and LMWH versus UFH. We summarised the results of each trial on an intention-to-treat basis in 2 x 2 tables for each outcome measurement. Where possible, all randomised participants were included, even if the original trial authors excluded them. The results obtained from different methods were similar (risk ratios, Mantel-Haenszel and Peto odds ratios), therefore the meta-analysis was performed using odds ratios (ORs) with 95% confidence intervals (CIs).

Unit of analysis issues

The individual participant was the unit of analysis in all included studies.

Dealing with missing data

Analysis was performed on an intention-to-treat basis, including all participants randomised.

Assessment of heterogeneity

A test for heterogeneity examines the null hypothesis that all studies are evaluating the same effect. We obtained P values comparing the test statistic with a Chi² distribution. To help readers assess the consistency of results of studies in a meta-analysis, RevMan 5 software includes a method (I² statistic) that describes the percentage of total variation across studies due to heterogeneity rather than by chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity (Higgins 2003).

Assessment of reporting biases

To detect reporting bias we planned to construct funnel plots for meta-analyses that included at least 10 studies, as funnel plots with less than 10 studies lack the power to distinguish chance from real asymmetry.

Data synthesis

An heterogeneity test was performed and we planned to use a random-effects model if the test was positive (I² > 50%); unless otherwise stated the meta-analysis was performed using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

Where data were available, subgroup analysis was performed to evaluate outcomes based on medical diagnosis at hospital admission.

Sensitivity analysis

Four studies included in the review had a loss of ≥ 20% of the study population between randomisation and evaluation for DVT

or PE (CERTAIN 2010; CERTIFY 2010; Fraisse 2000; MEDENOX 1999). Although the majority of the missing participants were accounted for with suitable reasoning, it was still possible these losses could alter the outcome. Sensitivity analysis was performed by removing these studies from the DVT and PE outcomes and evaluating their effect on the meta-analysis.

DVT diagnosis using a fibrinogen uptake test and plethysmography is often less accurate than by ultrasound or venography. In order to establish that the meta-analysis results were not dependent on studies using these low-accuracy tests, sensitivity analysis was conducted by removing three studies using a fibrinogen uptake test or plethysmography to detect DVT (Belch 1981; Dahan 1986; EMSG 1996) and the effect evaluated.

The safety data for the CERTAIN 2010 study was collected after a three month follow-up period, which was different to the other studies that collected the efficacy and safety data during the same study time period. With this additional time allotted for these endpoints it was possible this study unduly altered the meta-analysis, therefore sensitivity analysis was performed by removing this study from the meta-analyses for major and minor bleeding, as well as thrombocytopenia, and evaluating the effect.

In two studies (Belch 1981; Dahan 1986) major bleeding was not defined, and was only described as 'major bleeding'. In order to determine if these studies with inadequate definitions of major bleeding were not having an overt effect on the meta-analysis they were removed in a sensitivity analysis to evaluate the effect.

Two studies (EMSG 1996; MEDENOX 1999) included a low-dosage (20 mg) of the LMWH enoxaparin. For EMSG 1996 this was the only LMWH dosage, but for MEDENOX 1999 there was also a higher dosage of 40 mg. Sensitivity analysis was performed by removing the 20 mg dosages and the effect was evaluated.

RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.

Included studies

For this update there were an additional three studies included ([CERTAIN 2010](#); [CERTIFY 2010](#); [LIFENOX 2011](#)). For details of the included studies see [Characteristics of included studies](#).

We included 16 studies (45 published articles) with 34,369 participants. Ten of these studies compared heparin prophylaxis with no treatment or placebo ([Belch 1981](#); [Bergmann 1996](#); [Dahan 1986](#); [Fraisie 2000](#); [Gallus 1973](#); [Gardlund 1996](#); [Ibarra-Perez 1988](#); [LIFENOX 2011](#); [MEDENOX 1999](#); [PREVENT 2004](#)) and six studies compared LMWH with UFH ([CERTAIN 2010](#); [CERTIFY 2010](#); [EMSG 1996](#); [Forette 1995](#); [PRIME 1996](#); [THE-PRINCE 2003](#)). Fifteen of the included studies were written in English, and one in French ([Forette 1995](#)) that we had translated.

Four trials took place in a single centre ([Belch 1981](#); [Dahan 1986](#); [Gallus 1973](#); [Ibarra-Perez 1988](#)). Nine trials were European multi-centre trials: four in France ([Bergmann 1996](#); [EMSG 1996](#); [Forette 1995](#); [Fraisie 2000](#)), one in Sweden ([Gardlund 1996](#)), three in Germany ([CERTAIN 2010](#); [CERTIFY 2010](#); [THE-PRINCE 2003](#)), and one in Germany and Austria ([PRIME 1996](#)). One trial was performed in multiple centres across Europe and Canada ([MEDENOX 1999](#)) and two trials were truly multi-national, one performed in centres across Europe, North and South America, Canada, North and Southern Africa, Israel, Lebanon and Australia ([PREVENT 2004](#)) and the other in China, India, Korea, Malaysia, Mexico, Philippines and Tunisia ([LIFENOX 2011](#)).

Heparin versus placebo or no treatment

Four trials compared UFH with no treatment ([Belch 1981](#); [Gallus 1973](#); [Gardlund 1996](#); [Ibarra-Perez 1988](#)). One study compared UFH 5000 IU twice daily ([Gardlund 1996](#)) and the other two studies compared UFH 5000 IU three times daily with no treatment ([Belch 1981](#); [Gallus 1973](#)).

Six trials compared LMWH with placebo, three trials were with enoxaparin ([Dahan 1986](#); [LIFENOX 2011](#); [MEDENOX 1999](#)), two trials with nadroparin ([Bergmann 1996](#); [Fraisie 2000](#)), and one trial with

dalteparin ([PREVENT 2004](#)). One of the enoxaparin trials ([MEDENOX 1999](#)) compared two doses (20 mg and 40 mg) of enoxaparin with placebo. For assessment of major and minor bleeding the maximum licensed duration of treatment was used.

LMWH versus UFH

Six trials compared LMWH with UFH ([CERTAIN 2010](#); [CERTIFY 2010](#); [EMSG 1996](#); [Forette 1995](#); [PRIME 1996](#); [THE-PRINCE 2003](#)). Three of these trials compared enoxaparin with UFH ([EMSG 1996](#); [PRIME 1996](#); [THE-PRINCE 2003](#)). Two trials compared enoxaparin 40 mg once daily with UFH 5000 IU three times daily ([PRIME 1996](#); [THE-PRINCE 2003](#)); one trial compared enoxaparin 20 mg once daily with UFH 5000 IU twice daily ([EMSG 1996](#)). One trial compared nadroparin 3075 antiXa units once daily with UFH 5000 to 7500 IU three times daily ([Forette 1995](#)). One trial compared certoparin 3000 antiXa units with UFH 5000 IU three times daily ([CERTIFY 2010](#)).

Excluded studies

For this update one additional study was excluded ([EXCLAIM](#)) and there were 10 ([Aquino 1990](#); [Cade 1982a](#); [Cade 1982b](#); [Halkin 1982](#); [Harenberg 1990](#); [HESIM](#); [Manciet 1990](#); [Mottier 1993](#); [Poniewierski 1988](#); [PROMPT](#)) from the original review. The reasons for exclusion are detailed in [Characteristics of excluded studies](#). In brief, one study did not strictly fit the criteria for a randomised control trial ([Halkin 1982](#)), six studies included patients meeting the exclusion criteria of MI (or acute coronary disease), recent surgery, stroke (or cerebrovascular disease) that could not be removed from the analysis ([Cade 1982a](#); [Cade 1982b](#); [Harenberg 1990](#); [HESIM](#); [Mottier 1993](#); [PROMPT](#)), two studies included patients receiving orthopaedic rehabilitation ([Aquino 1990](#); [Manciet 1990](#)), one study had all participants receiving the study medication before randomisation to continue the medication or move to placebo ([EXCLAIM](#)), and one study's method for identifying DVT was not considered sensitive enough ([PROMPT](#)).

Risk of bias in included studies

For details see [Figure 2](#); [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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Belch 1981	?	?	-	+	+	+	+
Bergmann 1996	?	?	+	?	+	?	+
CERTAIN 2010	+	+	-	+	?	+	?
CERTIFY 2010	+	+	+	+	+	+	?
Dahan 1986	?	?	+	?	+	+	+
EMSG 1996	+	+	+	+	+	+	+
Forette 1995	+	+	-	?	+	+	+
Fraisse 2000	?	?	+	+	+	+	?
Gallus 1973	?	+	-	?	+	+	+
Gardlund 1996	?	?	-	+	?	+	+
Ibarra-Perez 1988	?	?	-	?	?	+	+
LIFENOX 2011	+	+	+	+	+	+	?
MEDENOX 1999	?	+	+	+	+	+	?
PREVENT 2004	?	?	+	+	+	+	?
PRIME 1996	?	?	+	?	+	+	+
THE-PRINCE 2003	?	?	-	?	?	+	?

Allocation

For random sequence generation five studies were considered low risk (CERTAIN 2010; CERTIFY 2010; EMSG 1996; Forette 1995; LIFENOX 2011) and the remaining 11 studies did not give enough information to determine how sequence generation was performed (Belch 1981; Bergmann 1996; Dahan 1986; Fraisse 2000; Gallus 1973; Gardlund 1996; Ibarra-Perez 1988; MEDENOX 1999; PREVENT 2004; PRIME 1996; THE-PRINCE 2003).

For allocation concealment, seven studies were considered to be low risk (CERTAIN 2010; CERTIFY 2010; EMSG 1996; Forette 1995; Gallus 1973; LIFENOX 2011; MEDENOX 1999) and the remaining nine studies did not give enough information to understand if allocation was properly concealed (Belch 1981; Bergmann 1996; Dahan 1986; Fraisse 2000; Gardlund 1996; Ibarra-Perez 1988; PREVENT 2004; PRIME 1996; THE-PRINCE 2003).

Blinding

Adequate blinding is important in reducing the chance of bias in the detection of DVT and PE. Nine trials used double blinding and were considered low risk for performance bias (Bergmann 1996; CERTIFY 2010; Dahan 1986; EMSG 1996; Fraisse 2000; LIFENOX 2011; MEDENOX 1999; PREVENT 2004; PRIME 1996). Seven trials were described as open or unblinded, and were therefore at high risk of performance bias (Belch 1981; CERTAIN 2010; Forette 1995; Gallus 1973; Gardlund 1996; Ibarra-Perez 1988; THE-PRINCE 2003).

In nine trials evaluation of the outcomes was undertaken by blinded assessors, and therefore had little risk of detection bias (Belch 1981; CERTAIN 2010; CERTIFY 2010; EMSG 1996; Fraisse 2000; Gardlund 1996; LIFENOX 2011; MEDENOX 1999; PREVENT 2004). Six trials did not indicate if the assessors were blinded and therefore had unclear detection bias (Bergmann 1996; Dahan 1986; Forette 1995; Gallus 1973; Ibarra-Perez 1988; PRIME 1996). For THE-PRINCE 2003 study the authors clearly stated that the efficacy endpoints were evaluated by blinded assessors and was therefore at low risk of detection bias, but the safety endpoints were not included in this description so they had an unclear risk of detection bias.

Incomplete outcome data

Twelve studies included all randomised participants in the analysis or clearly described how many participants were excluded from each group and why, and that the treatment groups remained similar after the exclusions (Belch 1981; Bergmann 1996; CERTIFY 2010; Dahan 1986; EMSG 1996; Forette 1995; Fraisse 2000; Gallus 1973; LIFENOX 2011; MEDENOX 1999; PREVENT 2004; PRIME 1996). These 12 studies were considered low risk for attrition bias. Two studies did not include enough information about incomplete outcome data to determine whether or not there was a risk of attrition bias (Gardlund 1996; Ibarra-Perez 1988). In the CERTAIN 2010 study the efficacy endpoints had unclear risk as there were missing participants unaccounted for in the analysis, but there was a low risk of attrition bias for the safety endpoints as all participants were considered in this analysis. For THE-PRINCE 2003 study the study authors described inequality between the study groups for the reasons why participants withdrew and were not included in the analysis, leading to high risk of attrition bias for these outcomes. However, the safety endpoints in this study were at a low risk of attrition bias because all participants were reported on.

Selective reporting

Fifteen of the 16 studies have low risk of reporting bias because they either followed the provided protocol or there was no evidence of selective outcome reporting. The Bergmann 1996 study was considered to have unclear risk of reporting bias because in the limited report available it was unclear whether the mortality reported was all-cause or specifically due to thromboembolism.

Other potential sources of bias

Seven studies reported support by large pharmaceutical companies, which could have potentially introduced bias (CERTAIN 2010; CERTIFY 2010; Fraisse 2000; LIFENOX 2011; MEDENOX 1999; PREVENT 2004; THE-PRINCE 2003).

Effects of interventions

Heparin (LMWH and UFH) versus placebo or no treatment

Efficacy

Deep vein thrombosis (DVT)

Data were available for DVT in seven trials (Belch 1981; Dahan 1986; Fraisse 2000; Gallus 1973; Ibarra-Perez 1988; MEDENOX 1999; PREVENT 2004). The heparin treatment group had reduced odds of DVT (OR 0.41; 95% CI 0.25 to 0.67; $P = 0.0004$). When sensitivity analysis was performed to assess the effects of a loss of $\geq 20\%$ of the study population, the Fraisse 2000 and MEDENOX 1999 studies were removed and there was little effect on the results with an OR of 0.26 (95% CI 0.12 to 0.54; $P = 0.0004$). By removing Belch 1981 and Dahan 1986 for sensitivity analysis for low-accuracy testing of DVT there was little effect on the overall outcome with an OR of 0.48 (95% CI 0.29 to 0.81; $P = 0.006$). Removing the low-dose enoxaparin group from the MEDENOX 1999 study, there was only a slight variation in the analyses (OR 0.37; 95% CI 0.25 to 0.55; $P < 0.00001$).

Pulmonary embolism (PE)

Symptomatic, non-fatal PE was measured in seven trials (Belch 1981; Dahan 1986; Fraisse 2000; Gardlund 1996; Ibarra-Perez 1988; MEDENOX 1999; PREVENT 2004). Meta-analysis was only conducted for six, excluding Gardlund 1996 as non-fatal PE was only assessed through necropsy data and not in all participants. Non-fatal PE had an OR of 0.46 (95% CI 0.20 to 1.07; $P = 0.07$). Fatal PE was recorded in six trials (Bergmann 1996; Dahan 1986; Gardlund 1996; LIFENOX 2011; MEDENOX 1999; PREVENT 2004) with an OR of 0.71 (95% CI 0.43 to 1.15; $P = 0.16$). Combined non-fatal PE and fatal PE was reported for nine studies (Belch 1981; Bergmann 1996; Dahan 1986; Fraisse 2000; Gardlund 1996; Ibarra-Perez 1988; LIFENOX 2011; MEDENOX 1999; PREVENT 2004) with an OR of 0.66 (95% CI 0.43 to 1.02; $P = 0.06$). When the Fraisse 2000 and MEDENOX 1999 studies were removed for sensitivity analysis to assess the effects of a loss of $\geq 20\%$ of the study population, there was little change in results for non-fatal PE (OR 0.55; 95% CI 0.22 to 1.39; $P = 0.20$), no change for fatal PE as neither study was contributing, and there was no difference between the treatment groups for combined non-fatal and fatal PE (OR 0.68 95% CI 0.44 to 1.07; $P = 0.09$). When the 20 mg enoxaparin treatment group in the MEDENOX 1999 study was removed there was a small change on non-fatal PE (OR 0.50; 95% CI 0.21 to 1.20; $P = 0.12$), no change for fatal PE, and almost no change for combined non-fatal and fatal PE (OR 0.66; 95% CI 0.43 to 1.03; $P = 0.07$).

All-cause mortality

All-cause mortality was assessed in eight trials ([Bergmann 1996](#); [Dahan 1986](#); [Fraisie 2000](#); [Gardlund 1996](#); [Ibarra-Perez 1988](#); [LIFENOX 2011](#); [MEDENOX 1999](#); [PREVENT 2004](#)) but meta-analysis was only performed for seven, excluding [Ibarra-Perez 1988](#) because not enough information was given to fully understand which treatment groups the deaths occurred in. There was no clear evidence of a difference in mortality between the two treatment groups, with an OR of 0.97 (95% CI 0.87 to 1.08; $P = 0.57$). When the [MEDENOX 1999](#) study's 20 mg enoxaparin treatment group was removed in a sensitivity analysis there was no change to the results of the analyses.

Safety

Bleeding

Major bleeding was evaluated in eight studies ([Belch 1981](#); [Dahan 1986](#); [Fraisie 2000](#); [Gardlund 1996](#); [Ibarra-Perez 1988](#); [LIFENOX 2011](#); [MEDENOX 1999](#); [PREVENT 2004](#)) but meta-analysis was conducted using only seven trials, excluding [Gardlund 1996](#). This was for the same reason as for the outcome of non-fatal PE: major bleeding was only evaluated through necropsy data and was not evaluated in all patients. Heparin was associated with an increase in major bleeding (OR 1.65; 95% CI 1.01 to 2.71; $P = 0.05$). When sensitivity analysis was performed by removing studies with inadequate definitions of the major bleeding, [Belch 1981](#) and [Dahan 1986](#), the association was more precise (OR 1.83; 95% CI 1.09 to 3.07; $P = 0.02$). Minor bleeding was evaluated in five studies ([Fraisie 2000](#); [Ibarra-Perez 1988](#); [LIFENOX 2011](#); [MEDENOX 1999](#); [PREVENT 2004](#)) and heparin was associated with significantly increased odds of 1.61 (95% CI 1.26 to 2.08; $P = 0.0002$). When the low dose of enoxaparin in the [MEDENOX 1999](#) study was removed, the major bleeding outcome had stronger statistical significance (OR 1.81; 95% CI 1.09 to 3.03; $P = 0.02$) but there was very little change in the minor bleeding outcome (OR 1.61; 95% CI 1.23 to 2.12; $P = 0.0006$).

Thrombocytopaenia

Thrombocytopaenia was measured in four studies ([Fraisie 2000](#); [LIFENOX 2011](#); [MEDENOX 1999](#); [PREVENT 2004](#)). There was no clear evidence of a difference between the two groups for thrombocytopaenia (OR 1.05; 95% CI 0.64 to 1.74; $P = 0.85$). Removing the low-dose enoxaparin treatment group from the [MEDENOX 1999](#) study had little effect on the overall outcome (OR 1.12; 95% CI 0.63 to 2.00; $P = 0.69$).

Heterogeneity and reporting bias

For the comparison between heparin and placebo or no treatment there was little or no heterogeneity between the studies, therefore all meta-analyses, except for the DVT outcome, were conducted using a fixed-effect model. The DVT outcome was analysed using a random-effects model but when the 20 mg enoxaparin treatment group in the [MEDENOX 1999](#) study was removed for sensitivity analysis a fixed-effect model was able to be utilised. None of the comparisons had 10 or more studies so an assessment for reporting bias by constructing funnel plots could not be performed.

LMWH versus UFH

Efficacy

Deep vein thrombosis (DVT)

Six studies evaluated DVT ([CERTAIN 2010](#); [CERTIFY 2010](#); [EMSG 1996](#); [Forette 1995](#); [PRIME 1996](#); [THE-PRINCE 2003](#)). For the LMWH treatment group there was a decreased odds compared to the UFH group (OR 0.77; 95% CI 0.62 to 0.96; $P = 0.02$). When the [CERTAIN 2010](#) and [CERTIFY 2010](#) were removed for sensitivity analysis to assess the effects of a loss of $\geq 20\%$ of the study population, there was no longer any evidence of a difference between the treatment groups (OR 0.80; 95% CI 0.50 to 1.29; $P = 0.37$). Removing [EMSG 1996](#) for sensitivity analysis for both a low-accuracy test for DVT and low dosage of enoxaparin, there was very little effect on the overall outcome (OR 0.76; 95% CI 0.61 to 0.96; $P = 0.02$).

Pulmonary embolism (PE)

Symptomatic, non-fatal PE was measured in six studies ([CERTAIN 2010](#); [CERTIFY 2010](#); [EMSG 1996](#); [Forette 1995](#); [PRIME 1996](#); [THE-PRINCE 2003](#)). There was no clear evidence of a difference between LMWH and UFH for non-fatal PE (OR 0.93; 95% CI 0.42 to 2.08; $P = 0.86$). Fatal PE was measured in only two studies ([CERTAIN 2010](#); [CERTIFY 2010](#)) for which there was no difference between the two treatment groups (OR 0.33; 95% CI 0.01 to 8.13; $P = 0.50$). Combined non-fatal and fatal PE was evaluated in the same six studies as non-fatal PE, with no evidence of a difference between UFH and LMWH (OR 0.86; 95% CI 0.39 to 1.90; $P = 0.71$). When [CERTAIN 2010](#) and [CERTIFY 2010](#) were removed for sensitivity analysis to assess the effects of a loss of $\geq 20\%$ of the study population, the non-fatal PE OR was lowered to 0.47, but the association remained non-significant (95% CI 0.13 to 1.68; $P = 0.25$). As [CERTAIN 2010](#) and [CERTIFY 2010](#) were the only two studies evaluated for fatal PE, this outcome was no longer estimable and the combined non-fatal and fatal PE was identical to non-fatal PE.

All-cause mortality

All-cause mortality was assessed in five studies ([CERTIFY 2010](#); [EMSG 1996](#); [Forette 1995](#); [PRIME 1996](#); [THE-PRINCE 2003](#)). There was no clear evidence for a difference in mortality (OR 0.79; 95% CI 0.54 to 1.16; $P = 0.23$).

Safety

Bleeding

Six studies measured major bleeding as an outcome ([CERTAIN 2010](#); [CERTIFY 2010](#); [EMSG 1996](#); [Forette 1995](#); [PRIME 1996](#); [THE-PRINCE 2003](#)). There was a reduced odds found in the LMWH group compared with the UFH group (OR 0.43; 95% CI 0.22 to 0.83; $P = 0.01$). Minor bleeding was assessed in three studies ([CERTAIN 2010](#); [CERTIFY 2010](#); [Forette 1995](#)) and was associated with an imprecise decreased odds with LMWH (OR 0.70; 95% CI 0.48 to 1.00; $P = 0.05$), possibly a chance effect. When the [CERTAIN 2010](#) study was removed for sensitivity analysis to assess the effect of the longer follow-up time period, there was little change for major bleeding (OR 0.43; 95% CI 0.22 to 0.87; $P = 0.02$) and minor bleeding moved from a possible chance effect to statistically significant (OR 0.66; 95% CI 0.45 to 0.96; $P = 0.03$).

Thrombocytopaenia

Thrombocytopaenia was evaluated in three studies ([CERTAIN 2010](#); [CERTIFY 2010](#); [Forette 1995](#)). There was no difference between

LMWH and UFH (OR 0.41; 95% CI 0.08 to 2.11; $P = 0.28$). When sensitivity analysis was performed by removing the [CERTAIN 2010](#) study to assess the effects of the longer follow-up period, there was very little change (OR 0.43; 95% CI 0.06 to 2.92; $P = 0.39$).

Heterogeneity and reporting bias

For the comparison between UFH and LMWH there was little or no heterogeneity between the studies, therefore all meta-analyses were conducted using a fixed-effect model. None of the comparisons had 10 or more studies so an assessment for reporting bias by using a funnel plot could not be performed.

Subgroup analysis

Subgroup analysis based on medical diagnosis at hospital admission could not be performed as there are currently insufficient data within published studies on outcomes within subgroups of interest.

DISCUSSION

Summary of main results

Heparin resulted in a reduction in DVT but no difference in non-fatal and/or fatal PE (separately and combined) when compared with placebo or no treatment. The reduction in VTE risk is comparable to that previously reported in prophylaxis studies of patients following acute myocardial infarction ([Collins 1996](#)), acute ischaemic stroke ([Gubitz 2004](#)), colorectal surgery ([Wille-Jørgensen 2004](#)) and orthopaedic surgery ([Collins 1988](#)).

The analysis found no clear difference in all-cause mortality in patients receiving heparin prophylaxis. However, these studies are not powered to show a difference in mortality, which would require over 200,000 patients (assuming an overall 5% mortality, 10% of deaths due to VTE, and a 50% relative risk (RR) reduction in events).

In the presence of heparin prophylaxis the rate of major haemorrhage (0.64%) was higher than with no prophylaxis (0.36%). LMWH resulted in less major haemorrhage than UFH. This suggests a favourable benefit-risk ratio for LMWH therapy in the prevention of VTE in general medical patients.

In summary, patients hospitalised with an acute medical illness who receive UFH or LMWH thromboprophylaxis have a reduced risk of DVT, however there is an increase in major haemorrhage when compared to those who do not receive chemical thromboprophylaxis. LMWH reduced the odds of DVT compared with UFH as well as reduced the odds of major bleeding, suggesting LMWH has a better efficacy profile and carries a lower risk of adverse events compared with UFH. There are currently insufficient published data to allow analysis of outcomes of interest based on patient medical diagnosis at hospital admission.

Overall completeness and applicability of evidence

The conclusions provided in this analysis have a strong external application as the evidence was generated using 16 good quality studies that were sufficient to address the study outcomes. The 16 studies included 34,369 participants from at least 17 different countries, with the majority of studies being multi-centre, and four being multi-national.

Although this review does not identify heparin as preventing all-cause mortality in patients with an acute medical illness, it does appear to show a benefit in reducing DVT and possibly the combined outcome of symptomatic PE and fatal PE. Therefore, in patients with an acute medical illness heparin appears to reduce the risk of hospital acquired thrombosis (HAT), supporting the current medical practice of increasing awareness and advocating VTE prevention ([NICE](#)).

Currently, published studies are lacking outcome data specific to medical diagnosis at hospital admission. These data would help us to understand if certain patients, based on disease, would benefit more or less from thromboprophylaxis or are at a higher or lower risk of bleeding. Understanding these differences would help develop a stronger profile for the use of thromboprophylaxis in acutely ill medical patients.

Patients who develop VTE following an acute medical illness have a more severe presentation and significantly worse outcome than patients who develop VTE following surgery ([Monreal 2004](#)). Venous thromboembolic disease in hospitalised medical patients is a preventable occurrence and is associated with unacceptably high levels of morbidity and mortality.

In a report by the House of Commons Health Committee, it was recommended that "VTE and its prevention, including the implementation of, and adherence to guidelines relating to thromboprophylaxis, counselling and risk assessment, be given more prominence in undergraduate medical education, continuing professional development, and other relevant aspects of medical and paramedical training" ([Health Committee 2005](#)).

The current 'Prevention of VTE' guidelines presented by the American College of Chest Physicians also stress the importance of all hospitals having formal, written guidelines for thromboprophylaxis and that all patients undergo VTE risk assessment ([Kahn 2012](#)).

Current medical practice concerning VTE emphasizes awareness of HAT, with appreciation for the risk of VTE increasing dramatically within the past decade. All patients admitted to hospital with an acute medical illness should be risk assessed and thromboprophylaxis offered to those perceived to be at increased risk of VTE. In fact, patients are actively encouraged to question their admitting physicians as to their individual VTE risk and need for thromboprophylaxis ([NICE](#)) in an attempt to reduce the risk of HAT.

Quality of the evidence

Sixteen studies were used to compile evidence, 10 comparing heparin prophylaxis with no treatment or placebo and six which compared LMWH to UFH, with a total of 34,369 participants. For the majority of the outcomes there was general agreement between the studies. Overall quality of the studies was good, with concern for performance bias in the studies that were open label, which made up just under half of the studies. Also, most of the studies were lacking in an explanation of how random sequence generation and allocation concealment were performed, although this is most likely due to the fact that many included studies are older and were not held to as high reporting standards when published.

Potential biases in the review process

All data used were dichotomous, therefore little data manipulation that could introduce bias was required for analysis. However, for the [Bergmann 1996](#) study all-cause mortality data were calculated using provided percentages and were transformed into dichotomous values for the purposes of the meta-analysis.

In order to reduce bias, both the 20 mg and 40 mg enoxaparin groups from [MEDENOX 1999](#) were included in the meta-analysis. To avoid double-counting of participants, the participants and events within the comparison (placebo) group were split evenly between the two treatment groups, rounding down for odd numbers.

While all attempts to include relevant studies were made by the review authors, it is possible pertinent data were overlooked.

Agreements and disagreements with other studies or reviews

Several meta-analysis are available on this topic.

Mismetti 2000

The findings of this review are in keeping with the meta-analysis published by Mismetti et al, which assessed seven trials comparing prophylactic heparin to control and nine trials comparing UFH with LMWH ([Mismetti 2000](#)). The meta-analysis found a statistically significant decrease in DVT (RR 0.44; 95% CI 0.29 to 0.64; $P < 0.001$) and clinical PE (RR 0.48; 95% CI 0.34 to 0.68; $P < 0.001$) when heparin was compared to control, which are consistent with our review, although Mismetti identified a stronger relationship with PE as our findings for non-fatal and fatal PE were imprecise and possibly due to chance effect. The Mismetti review found no difference in mortality, the same as our review, but they also found no difference in major bleeding, which is inconsistent with our review. No difference was observed in efficacy between UFH and LMWH in the Mismetti review, but our review found a decrease in DVT favouring LMWH. Also, our review found a decrease in major bleeding favouring LMWH, which is consistent with the Mismetti review findings.

The Mismetti review used six of the same studies as we did for the comparison of heparin to control ([Belch 1981](#); [Bergmann 1996](#); [Dahan 1986](#); [Fraisie 2000](#); [Gardlund 1996](#); [Ibarra-Perez 1988](#)) and one study which was excluded from our review. For the comparison between UFH and LMWH, the Mismetti study analysed four studies used in our review ([EMSG 1996](#); [Forette 1995](#); [PRIME 1996](#); [THE-PRINCE 2003](#)) and five studies that we excluded. While the authors described that they excluded cases of acute ischaemic stroke and acute myocardial infarction some of the studies included patients with acute coronary disease that could not be removed for analysis. Other criteria that warranted exclusion in our review were not upheld in the Mismetti review, such as detection method and inclusion of surgical patients, which led to differences in the profile of the included studies and the minor differences seen in the results.

Dentali 2007

A meta-analysis by Dentali et al assessed anticoagulant prophylaxis (UFH, LMWH and fondaparinux) to prevent symptomatic VTE in hospitalised medical patients ([Dentali 2007](#)). Nine trials were included in this analysis. Anticoagulant prophylaxis was associated

with a borderline risk reduction in DVT (RR 0.47; 95% CI 0.22 to 1.00), which is consistent with this review. The Dentali review found a reduction in all PE (RR 0.43; 95% CI 0.26 to 0.71) for the prophylaxis group, but our review found no difference in non-fatal and fatal PE. It was also noted in the Dentali review that anticoagulant prophylaxis was associated with a RR 1.32 (95% CI 0.73 to 2.37) for major bleeding, where our review found a statistically significant increase in major bleeding (OR 1.81; 95% CI 1.10 to 2.98; $P = 0.02$).

The Dentali review considered seven of the same studies that we included in this review for the comparison between anticoagulant prophylaxis and control ([Belch 1981](#); [Bergmann 1996](#); [Dahan 1986](#); [Fraisie 2000](#); [Gardlund 1996](#); [MEDENOX 1999](#); [PREVENT 2004](#)) and two studies considered not relevant or excluded from our review. Although study inclusion and exclusion criteria were similar for the Dentali review and this review, the minor differences led to the different study profile and variations in results. A major difference is that the Dentali review included studies that observed effects of fondaparinux, and not solely heparin. Also, one included study did contain participants with a recent myocardial infarction, which excluded it from the current review.

Bump 2009

A meta-analysis published in 2009 by Bump et al compared heparin prophylaxis to control in seven studies, and LMWH to UFH in six studies ([Bump 2009](#)). Comparing heparin versus control, the authors found a decreased risk of all DVT, with a RR of 0.55 (95% CI 0.36 to 0.83), and all PE, with a RR of 0.70 (95% CI 0.53 to 0.93) in the heparin treatment group, but no difference in mortality between the groups (RR 0.92; 95% CI 0.82 to 1.03). The findings on all DVT and all-cause mortality are consistent with our review, but our review found did not find a difference in non-fatal and fatal PE. The Bump review did not find a difference between heparin and control for major bleeding, but in our review we found major bleeding to be significantly increased in the heparin group. For the studies comparing LMWH to UFH there were no statistically significant differences between the two treatment groups for DVT, PE, death or bleeding. The data on PE and death are consistent with our review, but we found a decrease in DVT and major bleeding favouring LMWH.

For the comparison between heparin and control the Bump et al review included six of the same studies as in our review ([Belch 1981](#); [Bergmann 1996](#); [Dahan 1986](#); [Gardlund 1996](#); [MEDENOX 1999](#); [PREVENT 2004](#)) with the addition of two studies that we excluded or considered not relevant. Comparing UFH to LMWH the Bump review included three of the same studies as in our review ([EMSG 1996](#); [PRIME 1996](#); [THE-PRINCE 2003](#)) with two extra studies which were excluded from our review. Although the Bump review sought to exclude trials predominantly made up of stroke or acute myocardial infarction patients, it did include studies that had some of these types of participants that could not be separated out for statistical purposes. This difference, along with the review being conducted before some of the big trials included in our review were published, has lead to a different profile of included studies and variations in results.

Lederle 2011

A more recent meta-analysis published by Lederle et al analysed 10 studies that compared prophylaxis with heparin or related agents to no heparin and nine studies comparing LMWH with UFH,

all in hospitalised medical patients ([Lederle 2011](#)). The review also analysed stroke patients, but this was performed separately and is not considered here. For studies that compared heparin prophylaxis with no heparin, a statistically significant decrease in PE was found in the heparin group with an OR of 0.69 (95% CI 0.52 to 0.90; $P = 0.006$), but our review found no difference in non-fatal and fatal PE. In the Lederle review there were no differences found for symptomatic DVT, fatal PE or all-cause mortality. The fatal PE and all-cause mortality results are consistent with our review, but DVTs were found to be statistically decreased in the heparin group compared to the placebo or no treatment group. No difference in major bleeding was observed in the Lederle review (OR 1.49; 95% CI 0.91 to 2.43; $P = 0.110$), whereas in our review the increase in major bleeding in the heparin arm was statistically significant. No differences were found between LMWH and UFH for efficacy or safety outcomes, but in our review we found a statistically significant decrease in both DVT and major bleeding favouring LMWH.

The Lederle review considered seven of the same studies as in the current review for the comparison between heparin and placebo or no treatment ([Belch 1981](#); [Bergmann 1996](#); [Dahan 1986](#); [Fraisie 2000](#); [Gardlund 1996](#); [MEDENOX 1999](#); [PREVENT 2004](#)), with the addition of three studies which were either considered not relevant or excluded from the current review. For the comparison between UFH and LMWH the Lederle review used five of the same studies as in our review ([CERTAIN 2010](#); [CERTIFY 2010](#); [MSG 1996](#); [PRIME 1996](#); [THE-PRINCE 2003](#)), with the addition of four studies that we either considered not relevant or excluded. The Lederle review extended inclusion to studies with common treatments for VTE, and not strictly heparin (which led to the inclusion of a study evaluating fondaparinux), and while studies including only acute myocardial infarction patients were excluded in the Lederle review it did include studies that had some acute coronary syndrome patients, which would have been excluded from our review. Also, the Lederle review was conducted before several newer studies were published that have been included in the current review. These differences can account for the variations in findings regarding both the heparin versus no heparin and UFH versus LMWH comparisons.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from this systematic review indicates that heparin (LMWH and UFH) thromboprophylaxis reduces the risk of DVT in patients

with an acute medical illness (excluding stroke and myocardial infarction). The benefit of a reduction in venous thromboembolic events has to be balanced against a potential increase in the risk of bleeding. The risks of DVT and major bleeding are reduced with LMWH compared with UFH, indicating LMWH to be superior to UFH.

Implications for research

Medical patients in the trials included in this review received thromboprophylaxis for between six to 28 days; at present the optimum duration of prophylaxis is unknown but most guidelines recommend between six to 14 days following admission to hospital with an acute medical illness, or during the hospital stay or time of immobilisation ([Kahn 2012](#)). Autopsy studies have identified patients suffering a fatal PE up to six weeks after an acute medical illness ([Alikhan 2004](#)). The recently published [EXCLAIM](#) trial showed that LMWH administered for up to 38 days reduced the rates of VTE following discharge from hospital when compared to placebo, but this was associated with an increased risk of bleeding. Similar findings were found in two recent studies of extended thromboprophylaxis in medical patients, the [ADOPT](#) trial showed a trend but no clear reduction in VTE and the [MAGELLAN](#) trial showed a significant reduction in VTE. Both studies showed increased bleeding with extended therapy ([ADOPT](#); [MAGELLAN](#)). These findings show that there are still questions, and little consensus, regarding optimal thromboprophylaxis duration and that further research is warranted in this area in order to determine how best to prevent VTE.

There are a number of emerging new oral direct anticoagulants which have been approved for use for thromboprophylaxis in elective orthopaedic hip and knee arthroplasty ([Ageno 2012](#)). However, studies in patients with an acute medical illness have found that the benefit of VTE reduction is outweighed by the increased risk of bleeding ([ADOPT](#); [MAGELLAN](#)). Future thromboprophylaxis studies should look to individualise thromboprophylaxis, offering it to patients at high risk of VTE and low risk of bleeding.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Belch 1981

Methods	Study design: single centre, randomised controlled trial with 2 parallel groups Intention-to-treat analysis: yes Country: Scotland, UK
Participants	Number: 100 (UFH n = 50; control n = 50) Age: (mean years) UFH 66.6; control 65.0 Sex: (M/F) UFH 35/15; control 34/16 Inclusion criteria: patients hospitalised with heart failure or chest infection, or both Exclusion criteria: iodine sensitivity, risk of bleeding, DVT or PE on admission, or confined to bed > 2 days prior to admission Reason for hospitalisation (n (%)): heart failure (UFH n = 21 (42.0), control n = 17 (34.0)); chest infection (UFH n = 18 (36.0), control n = 19 (38)); both (UFH n = 11 (22), control n = 14 (28))
Interventions	Treatment: UFH 5000 IU, subcutaneous injection, three times daily Control: no specific prophylaxis (no placebo injections) Duration: until fully mobile
Outcomes	DVT, PE, major and minor haemorrhage Haemorrhage definition: (major) not specified; (minor) not reported
Notes	Isotopically detected DVT (FUT at entry and every other day)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No matched placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	FUT scanning performed by a person unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis performed with all randomised participants, although no indication of loss to follow-up
Selective reporting (reporting bias)	Low risk	Report includes all expected outcomes, although no study protocol is available
Other bias	Low risk	The study appears to be free from other sources of bias

Bergmann 1996

Methods	Study design: multi-centre, randomised, double-blind controlled trial with 2 parallel groups Intention-to-treat analysis: yes
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Bergmann 1996 (Continued)

Country: France

Participants	Number: 2474 (nadroparin n = 1230; control n = 1244) Age (mean years): 76 Sex: not stated Inclusion criteria: patients hospitalised with acute medical illness and confined to bed Exclusion criteria: not stated Reason for hospitalisation: not described
Interventions	Treatment: LMWH (nadroparin) 7500 antiXa units, subcutaneous injection, once daily Control: placebo Duration: 21 days or discharge
Outcomes	PE, mortality
Notes	Autopsy documented PE Data on all-cause mortality was calculated from percentages provided in study paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind and control patients received matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data, although no indication of loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No description of the protocol; it is unclear whether mortality reported is all-cause or specifically due to thromboembolism
Other bias	Low risk	Study appears to be free from other sources of bias

CERTAIN 2010

Methods	Study design: multi-centre, randomised open-label, active-controlled trial Intention-to-treat analysis: efficacy outcomes no; safety outcomes yes Country: Germany
Participants	Number: 337 (certoparin n = 163; UFH n = 174)

Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction) (Review)

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CERTAIN 2010 (Continued)

Age: (mean years $\pm$ SD) total 70.6 ± 12.3 ; certoparin 70.2 ± 12.2 ; UFH 71.0 ± 12.4

Sex: M/F total 160/177; certoparin 77/86; UFH 83/91

Inclusion criteria: patient > 40 years, hospitalisation due to an acute non-surgical disease and significant recent decrease in mobility

Exclusion criteria: women of child bearing age unless post-menopausal or using a highly effective method of birth control, pregnancy or lactation, indication for anticoagulant / thrombolysis, major surgery or invasive procedure within 4 weeks prior to randomisation or expected within 2 weeks, immobilisation due to fracture of lower limb, acute ischaemic/haemorrhagic stroke, uncontrolled hypertension, active bleeding, active peptic ulcer, bleeding diathesis, pancreatic disease / malignant tumour with high risk of bleeding, endocarditis, thrombocytopaenia, severe renal / liver disease, history of addictive disorder, other investigational drug within 30 days or 5 half-lives before enrolment

Reason for hospitalisation (n (%)): not indicated which acute illnesses were included. Disease profile: diabetes (certoparin n = 52 (31.9), UFH n = 55 (31.6)); COPD (certoparin n = 42 (25.8), UFH n = 50 (28.7)); coronary artery disease (certoparin n = 26 (16.0); UFH n = 33 (19))

Interventions	<p>Treatment 1: Certoparin 3000 IU once daily</p> <p>Treatment 2: UFH 7500 IU twice daily</p> <p>Duration: 10 ± 2 days</p>
Outcomes	<p>Efficacy: composite of asymptomatic or symptomatic proximal / distal DVT, symptomatic PE or death related to VTE</p> <p>Safety: Major and minor bleeding during the study as well as during the 3 month follow-up</p> <p>Haemorrhage definition: (major) fatal bleeding, clinically overt bleeding associated with a fall of haemoglobin concentration > 20 g/L compared with baseline, requiring transfusion of 2 or more units of packed red cells or whole blood, retroperitoneal or intracranial bleeding or bleeding warranting treatment cessation; (minor) bleeding events not meeting major bleeding definition</p>
Notes	DVT assessed with the use of compression ultrasound

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list produced using a validated system. After confirming patient fulfilled inclusion /exclusion criteria, investigator telephoned a randomisation hotline
Allocation concealment (selection bias)	Low risk	Central allocation of assignment, participants and investigators could not foresee assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label administration of certoparin daily versus UFH twice daily
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcomes were verified by a blinded adjudication committee
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Efficacy outcomes missing 58 patients not included in reasons for exclusion; Safety outcomes are at low risk of attrition bias

CERTAIN 2010 (Continued)

Selective reporting (reporting bias)	Low risk	Study protocol is not available but detailed inclusion and exclusion criteria presented in paper and it is clear that the published report includes all expected outcomes
Other bias	Unclear risk	Funding of study supported by Novartis

CERTIFY 2010

Methods	Study design: multi-centre, randomised, double-blind study, controlled trial with 2 parallel groups Intention-to-treat analysis: yes Country: Germany
Participants	Number: 3241 (certoparin n = 1626; UFH n = 1615) Age: (mean years $\pm$ SD) total 78.8 $\pm$ 6.3; certoparin 79.0 $\pm$ 6.2; UFH 78.7 $\pm$ 6.3 Sex: (M/F) total 1324/1915; certoparin 669/955; UFH 655/960 Inclusion criteria: hospitalised medical patients, aged at least 70 years, with an acute medical illness with a significant decrease in mobility (bedridden or only able to walk short distances) expected for at least 4 days Exclusion criteria: immobilised for > 3 days prior to randomisation, those immobilised due to fracture or cast, expected to undergo major surgery or invasive procedure within 3 weeks of randomisation, severe sepsis or need for intubated ventilatory support, received LMWH > 48 hours in 5 days prior to randomisation, indications for anticoagulation or thrombolysis, life-expectancy < 6 months, presence of DVT / PE, non-haemorrhagic stroke < 3 months, haemorrhagic stroke < 12 months, intracranial disease, high-risk of GI bleeding, spinal/epidural anaesthesia < 12 hr, lumbar puncture < 12 hr, uncontrolled hypertension, severe liver or renal disease, acute endocarditis, active retinopathy, intravitreal / intraocular bleeding Reason for hospitalisation (n (%)): infections and infestations (certoparin n = 435 (26.8), UFH n = 458 (28.4)); cardiac disorders (certoparin n = 357 (22.0), UFH n = 362 (22.4)); respiratory, thoracic and mediastinal disorders (certoparin n = 280 (17.2), UFH n = 279 (17.3)); nervous system disorders (certoparin n = 115 (7.1), UFH n = 99 (6.1)); gastrointestinal disorders (certoparin n = 118 (7.3), UFH n = 95 (5.9)); vascular disorders (certoparin n = 92 (5.7), UFH n = 95 (5.9))
Interventions	Treatment 1: LMWH (certoparin) 3000 U Anti-Xa, subcutaneous injection, once daily, plus placebo twice daily Treatment 2: unfractionated heparin 5000 IU, subcutaneous injection, three times daily Duration: 8 - 20 days
Outcomes	Proximal DVT, symptomatic non-fatal PE, VTE-related mortality, all cause mortality, major and minor haemorrhage, thrombocytopenia Haemorrhage definition: (major) fatal bleeding, clinically overt bleeding associated with a fall in haemoglobin of more than 20 g/L from baseline, requiring a transfusion of two or more units of packed red cells or whole blood, bleeding in a critical area or organ; (minor) bleeding events that did not meet the major bleeding events
Notes	DVT assessed by compression ultrasound For the purposes of this analysis data collected during the treatment period was used

Risk of bias

CERTIFY 2010 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list was generated using a validated system that automates the random assignment of treatment arms to randomisation numbers in the specified ratio. Included patients were given the lowest number on the randomisation list
Allocation concealment (selection bias)	Low risk	Treatment assignment was concealed from patients and investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Certoparin was given once daily and UFH three times daily. Patients in the certoparin group received 2 additional placebo injections during the day, to match the regimen in the UFH group and to allow for treatment blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All parts of the endpoint were adjudicated by a blinded central adjudication and compression ultrasound reading centre
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient flow fully described, including discontinuations and losses to follow up. All patients who received trial medication were included in the safety evaluation
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the published report includes all the expected outcomes
Other bias	Unclear risk	Funding of study supported by Novartis

Dahan 1986

Methods	Study design: single centre, randomised, double blind, controlled trial with 2 parallel groups Intention-to-treat analysis: yes Country: France
Participants	Number: 270 (enoxaparin n = 135; placebo n = 135) Age: (mean years $\pm$ SD) enoxaparin 79.9 $\pm$ 6.8; placebo 80.1 $\pm$ 6.9 Sex: (M/F) enoxaparin 84/51; placebo 83/52. Inclusion criteria: patients > 65 years, hospitalised with acute medical illness. Exclusion criteria: ongoing anticoagulant or antiplatelet therapy; presence of active bleeding; presence of coagulation disorders; predictable short-term hospitalisation (< 7 days); iodine allergy. Reason for hospitalisation (n (%)): not given, but diagnoses of included patients were given: heart failure (LMWH n = 24 (17.8), control n = 25 (18.5)); respiratory diseases (LMWH n = 33 (24.4), control n = 24 (17.8)); ischaemic stroke (LMWH n = 19 (14.1), control n = 27 (20.0)); malignant diseases (LMWH n = 25 (18.5), control n = 10 (7.4)); diabetes (LMWH n = 4 (3.0), control n = 8 (5.9)); depression (LMWH n = 4 (3.0), control n = 6 (4.4)); syncope (LMWH n = 5 (3.7), control n = 8 (5.9)); infection (including chest) (LMWH n = 6 (4.4), control n = 5 (3.7)); neurologic diseases (LMWH n = 3 (2.2), control n = 4 (3.0)); joint diseases (LMWH n = 4 (3.0), control n = 7 (5.2)); hepatic or biliary diseases (LMWH n = 2 (1.5), control n = 2 (1.5)); miscellaneous (LMWH n = 3 (2.2), control n = 5 (3.7))
Interventions	Treatment: LMWH (enoxaparin) 60 mg in 0.3 ml, subcutaneous injection, once daily Control: placebo 0.3 ml, subcutaneous injection, once daily Duration: 10 days
Outcomes	DVT, PE, mortality, major haemorrhage

Dahan 1986 (Continued)

Haemorrhage definition: (major) "diffuse hemorrhage", not fully defined; (minor) not reported

Notes Isotopically detected DVT (I fibrinogen scanning at entry and every day or every other day) or documented symptomatic DVT or PE

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind and control patients received matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions were explained and were similar between groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the published report includes all the expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias

EMSG 1996

Methods	Study design: multi-centre, randomised, double blind, controlled trial with 2 parallel groups Intention-to-treat analysis: yes Country: France
Participants	Number: 442 (enoxaparin n = 217; UFH n = 225) Age: (years $\pm$ SEM) enoxaparin 83.8 ± 0.51 ; UFH 82.6 ± 0.46 Sex: M/F ratio enoxaparin 29%/71%; UFH 27%/73% Inclusion criteria: patients hospitalised with acute medical illness leading to reduced mobility Exclusion criteria: contraindication to anticoagulation; ongoing venous, arterial or cardiac disease requiring anticoagulation; history or allergy or thrombocytopaenia induced by UFH or LMWH; abnormal platelet count; any contraindication to isotopic or venographic investigations; renal disorders; local disorders of the lower limb that would interfere with FUT Reason for hospitalisation (n (%)): heart failure (enoxaparin n = 40 (18.5), UFH n = 46 (20.6)); bronchopulmonary infections (enoxaparin n = 49 (22.7), UFH n = 58 (26.0)); ischaemic stroke (enoxaparin n = 18 (8.3), UFH n = 20 (9.0)); cancer (enoxaparin n = 11 (5.1), UFH n = 19 (8.5)); malnutrition (enoxaparin n = 15 (6.9), UFH n = 18 (8.1)); dehydration (enoxaparin n = 39 (18.1), UFH n = 41 (18.4)); systemic infection (enoxaparin n = 8 (3.7), UFH n = 7 (3.1)); other (enoxaparin n = 125 (57.9), UFH n = 121 (54.3))
Interventions	Treatment 1: LMWH (enoxaparin) 20 mg, subcutaneous injection, once daily, plus placebo (mannitol) once daily Treatment 2: UFH 5000 IU, subcutaneous injection, twice daily

Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction) (Review)

EMSG 1996 (Continued)

Duration: 10 days

Outcomes	DVT, PE, mortality, major haemorrhage Haemorrhage definition: (major) clinical and associated with either a fall in haemoglobin 20 g/L, need for transfusion of two or more blood units, or if bleeding was retroperitoneal or intracranial; (minor) not reported
Notes	Isotopically detected DVT (FUT at entry and every day or every other day) or documented symptomatic DVT or PE

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Allocation concealment performed using a computer-generated randomisation schedule, and the code was unbroken
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, nurses and doctors were unaware of the treatment assigned to each patient...". Study treatment provided in pre-filled syringes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluation by blinded centralised interpreters
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data accounted for and unlikely to affect results
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the published report includes all the expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias

Forette 1995

Methods	Study design: multi-centre, randomised, open trial with 2 parallel groups Intention-to-treat analysis: yes Country: France
Participants	Number: 295 (nadroparin n = 146; UFH n = 149) Age: (mean years $\pm$ SD) nadroparin 82.8 $\pm$ 0.5; UFH 83.8 $\pm$ 0.6 Sex: (M/F) nadroparin 36/110; UFH 38/111 Inclusion criteria: patients hospitalised with acute medical illness for an estimated minimum duration of 4 weeks; recent transient reduced mobility; absence of a recent DVT confirmed by echo-Doppler 48 hours prior to inclusion in the study Exclusion criteria: previous reduced mobility; existence of echo-Doppler confirmed DVT prior to entry into study; previous DVT (within the last 6 months) or PE (within the last year); surgical intervention (non-orthopaedic 8 days; orthopaedic 28 days); cerebral haemorrhage within the previous 6 months or any neurosurgical intervention; renal insufficiency; severe liver disease, severe arterial hypertension; contraindication to heparin, or venographic or angiographic investigations; patients receiving aspirin, ticlopidine, anti-inflammatories, heparinoid or vitamin K

Forette 1995 (Continued)

Reason for hospitalisation (n (%)): all participants hospitalised with transient locomotor disability, no further description

Interventions	Treatment 1: LMWH (nadroparin) 3075 antiXa units, subcutaneous injection, once daily Treatment 2: UFH 5000 to 7500 IU, subcutaneous injection, three times daily Duration: 28 days
Outcomes	DVT, PE, mortality, major and minor haemorrhage, thrombocytopenia Haemorrhage definition: (major) requiring the cessation of treatment, such as retroperitoneal, digestive track bleeding with haematemesis or melena; (minor) events not requiring cessation of treatment, such as haematoma at injection site microscopic haematuria or benign epistaxis
Notes	Documented symptomatic DVT or PE by Doppler ultrasound

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by drawing of lots
Allocation concealment (selection bias)	Low risk	Allocation using sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described and an open study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data accounted for and unlikely to affect results
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the published report includes all the expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias

Fraisse 2000

Methods	Study design: Phase III, multi-centre, randomised, double blind trial, with 2 parallel groups Intention-to-treat analysis: yes Country: France
Participants	Number: 223 (nadroparin n = 109; placebo n = 114) Age: (mean years $\pm$ SD) nadroparin 69.4 $\pm$ 7.7; placebo 66.8 $\pm$ 8.2 Sex: (M/F) nadroparin 87/22; placebo 87/27 Inclusion criteria: patients age 40 to 80 years; hospitalised with COPD Exclusion criteria: confirmed DVT within previous 6 months; Doppler-confirmed DVT at inclusion to study; gastroduodenal ulcer; recent haemorrhagic CVA; severe liver failure; severe renal impairment; confirmed or uncontrolled hypertension; congenital or acquired coagulation disorder; history of hyper-

Fraisse 2000 (Continued)

sensitivity or thrombocytopaenia to heparins of any type; contraindications to anticoagulant therapy, venography or angiography; receiving aspirin, ticlopidine or oral anticoagulants

Reason for hospitalisation (n (%)): all participants had COPD

Interventions	Treatment: LMWH (nadroparin) 3800 to 5700 antiXa units, subcutaneous injection, once daily Control: placebo (0.9% saline), subcutaneous injection, once daily Duration: until patient weaned from mechanical ventilation, not exceeding 21 ± 1 days
Outcomes	DVT, PE, mortality, major and minor haemorrhage, thrombocytopaenia Haemorrhage definition: (major) overt, associated with a decrease in haemoglobin of 20 g/L compared with baseline, necessitated a transfusion of two or more units of packed red cells, retroperitoneal or intracranial, when the investigator decided to end the treatment with heparin because of benefit.risk ratio; (minor) bleeding not considered major
Notes	DVT detection before and every 7 days until end of study; Venography at end of treatment or documented symptomatic DVT or PE

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind and use of a matched placebo control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	DVT diagnosis confirmed by two blinded, independent radiological experts; adverse events confirmed by blinded Critical Events committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data accounted for and unlikely to affect results
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the published report includes all the expected outcomes; methods intended for assessing the outcome was unclear
Other bias	Unclear risk	Funding of study supported by Sanofi

Gallus 1973

Methods	Study design: single centre, randomised trial with 2 parallel groups Intention-to-treat analysis: yes Country: Canada
Participants	Number: 350 (UFH n = 169; control n = 181) Age (medical patients): (mean years) UFH 65 (range 44-83); control 63 (range 43-85) Sex: (M/F) UFH 28/10; control 31/9

Gallus 1973 (Continued)

Inclusion criteria: > 40 years old; admitted for elective surgery, emergency surgery after fracture of the femoral neck, and medical patients suspected of having myocardial infarction admitted to a coronary and intensive medical-care ward

Exclusion criteria: bleeding tendency; iodine allergy; history of DVT or PE within the previous year

Reason for hospitalisation (n (%)): all included participants hospitalised for heart failure

Interventions	Treatment: UFH 5000 IU, subcutaneous, three times daily Control: no specific prophylaxis (no placebo injections) Duration: until mobile
Outcomes	DVT, PE
Notes	Isotopically detected DVT (FUT at entry, daily for first 4 days, and every 2nd day after that), confirmed by venography For the purposes of this analysis, only participants hospitalised with heart failure were considered, Number: 26 (UFH n = 11; control n = 15)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No indication of blinding or use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis performed using all randomised participants, although no indication of loss to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the published report includes all the expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias

Gardlund 1996

Methods	Study design: multi-centre, randomised, unblinded, controlled trial, with 2 parallel groups Intention to treat: yes Country: Sweden
Participants	Number: 11693 (UFH n = 5776; control n = 5917) Age: (mean years) 75.0

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Gardlund 1996 (Continued)

Sex: (M/F) not reported

Inclusion criteria: aged ≥ 55 years; admitted to departments of infectious diseases

Exclusion criteria: pre-existing anticoagulant treatment; readmission within 60 days of randomisation; ability to be mobile; assessment of contraindications not possible; persistent haemorrhage or increased risk of bleeding complication; heparin prophylaxis judged to be indicated by the responsible doctor; severe renal failure or liver failure; HIV infection; terminal disease in which active treatment was withheld; data not available

Reason for hospitalisation (n (%)): pneumonia (UFH n = 1617 (28.0), control n = 1646 (27.8)); skin and soft-tissue infections (UFH n = 1063 (18.4), control n = 1114 (18.8)); fever/sepsis (UFH n = 767 (13.3), control n = 843 (14.2)); urinary-tract infection (UFH n = 560 (9.7), control n = 586 (9.9)); gastroenteritis (UFH n = 517 (8.9), control n = 505 (8.5)); upper-respiratory-tract infection (UFH n = 461 (8.0), control n = 436 (7.4)); bone/joint infection (UFH n = 258 (4.5), control n = 253 (4.3)); skin rash/eruption (UFH n = 144 (2.5), control n = 144 (2.4)); meningitis (UFH n = 77 (1.3), control n = 70 (1.2)); liver disease (UFH n = 22 (0.4), control n = 30 (0.5)); other infectious disease (UFH n = 185 (3.2), control n = 165 (2.8)); other non-infectious disease (UFH n = 105 (1.8), control n = 125 (2.1))

Interventions	Treatment: 5000 IU standard sodium heparin, subcutaneous injection the abdominal area, every 12 hours Control: no prophylactic treatment (no placebo injections) Duration: maximum 21 days
Outcomes	primary endpoint was necropsy-verified PE of a size likely to lead to death
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study described as unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Necropsy performed by pathologist blinded to treatment group. Significance of necropsy finding assessed by investigator unaware of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No discussion of control dropout, due to study design, so cannot compare attrition rates between study groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the published report includes all the expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias

Ibarra-Perez 1988

Methods	<p>Study design: single centre, randomised, open trial with five parallel groups</p> <p>Intention to treat: not indicated</p> <p>Country: Mexico</p>
Participants	<p>Number: 193 (heparin n = 39; GCS n = 39; EB n = 33; ASA n = 35; control n = 46)</p> <p>Age: (mean years) heparin 64.2; GCS 66.5; EB 65.7; ASA 62.5; control 62.2</p> <p>Sex: (M/F) heparin 22/17; GCS 20/19; EB 14/19; ASA 18/17; control 23/23</p> <p>Inclusion criteria: ≥ 40 years; pulmonary disease likely to enforce bed rest for three consecutive days or more</p> <p>Exclusion criteria: patient's or physician's refusal to cooperate or rejection of the preventive method; PE, DVT, medical history of PE or DVT; clinical haemorrhage from any source; cerebrovascular accident; vasculitis; pericarditis; coagulation disorders; use of antithrombotic agents; recent postoperative status; allergy to iodine</p> <p>Reason for hospitalisation (n (%)): all participants with pulmonary disease (COPD: UFH n = 23 (59.0), control n = 25 (54))</p>
Interventions	<p>Treatment 1: heparin 5000 IU, subcutaneous injections, every 12 hours</p> <p>Treatment 2: GCS worn 24 hours a day</p> <p>Treatment 3: EB reapplied every 8 - 12 hours</p> <p>Treatment 4: ASA 0.5 g, orally, twice daily</p> <p>Control: passive exercise and massage of lower extremities every 2 hours</p> <p>Duration: Until patients were ambulatory (range 3 - 44 days)</p>
Outcomes	<p>DVT, PE, all-cause mortality, major and minor bleeding</p> <p>Haemorrhage definition: (major) not specifically defined, but patients with gastrointestinal bleeding were considered major bleeding; (minor) not specifically defined, but patients with ecchymosis and petechiae were considered minor bleeding</p>
Notes	<p>DVT was detected using venography, venous Doppler, strain gauge plethysmography, fibrinogen uptake test and diagnosed using phlebogram</p> <p>PE diagnosed by perfusion and ventilation lung scans</p> <p>For the purposes of this analysis only the heparin and control populations are considered. Although the study reports an initial 221 participants, only 192 are considered for analysis, as the 29 discharged patients were not indicated as randomised, and if they were, no information was given on which treatment group they were in</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	First 50 participants were assigned to the control group, and the remaining were assigned at random, but no description of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment

Ibarra-Perez 1988 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as an open experiment with no matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	29 participants were discharged for described reasons, but not from which treatment group
Selective reporting (reporting bias)	Low risk	Report includes all expected outcomes, although no protocol is available
Other bias	Low risk	The study appears to be free from other sources of bias

LIFENOX 2011

Methods	Study design: multi-centre, double-blind, placebo-controlled randomised trial, with 2 parallel groups Intention-to-treat analysis: yes Countries: China, India, Korea, Malaysia, Mexico, Philippines, Tunisia
Participants	Number: 8319 (enoxaparin n = 4174; placebo n = 4145) Age: (mean years $\pm$ SD) enoxaparin 65.6 $\pm$ 12.0; placebo 65.3 $\pm$ 12.2 Sex: (M/F) enoxaparin 2603/1568; placebo 2608/1528 Inclusion criteria: male or female $\geq$ 40 years-old; hospitalised within 48 hours of randomisation with at least one of the following: acute decompensated heart failure, active cancer (diagnosis within 6 months) - unless hospitalised for chemotherapy, or severe systemic infection and at least one of chronic pulmonary disease / obesity (BMI > 30) / previous VTE / age > 60; anticipated duration of hospitalisation at least 6 days; health status: American Society of Anesthesiologists Health status score $\leq$ 3, Eastern Cooperative Oncology Group performance status $\leq$ 2 in cancer patient; anticipated life expectancy > 1 week; signed written informed consent Exclusion criteria: major surgery or major trauma within the previous 6 weeks; need for any ventilatory support; symptomatic VTE at enrolment; multi organ failure; evidence of an active bleeding disorder; contraindication to anticoagulation; cerebrovascular accident at inclusion and within 10 days prior study inclusion; prosthetic heart valves; confirmed cerebral metastases; known hypersensitivity to heparin or LMWH, or pork-derived products; history of documented episode of heparin or LMWH induced thrombocytopenia and/or thrombosis (HIT, HAT, or HITTS); participating in another clinical trial within the previous 30 days; persistent renal failure; known or suspected severe anaemia of unexplained cause considered clinically relevant by investigator; spinal or epidural analgesia or lumbar puncture within the preceding 24 hours; unlikely to be compliant (e.g. alcohol, drug abuse); women of childbearing potential not protected by effective contraceptive method of birth control and/or who are unwilling to be tested for pregnancy; refusal or inability to give informed consent to participate in the study; inability to be followed-up after discharge until day 90 after randomisation Reason for hospitalisation (n (%)): heart failure (enoxaparin n = 1280 (30.7), control n = 1297 (31.4)); severe systemic infection (enoxaparin n = 2383 (57.2), control n = 2336 (56.5)); active cancer (enoxaparin n = 195 (4.7), control n = 170 (4.1)); heart failure and systemic infection (enoxaparin n = 253 (6.1), control n = 262 (6.3)); heart failure and active cancer (enoxaparin n = 7 (0.2), control n = 5 (0.1)); severe systemic infection and active cancer (enoxaparin n = 45 (1.1), control n = 62 (1.5)); heart failure, severe

LIFENOX 2011 (Continued)

systemic infection and active cancer (enoxaparin n = 3 (0.1), control n = 2 (< 0.1)); none of the above (enoxaparin n = 24 (0.6), control n = 25 (0.6))

Interventions	<p>Treatment: enoxaparin 40 mg, subcutaneous injection daily</p> <p>Control: placebo (0.9% saline), subcutaneous injection daily</p> <p>Duration: 10 ± 4 days</p>
Outcomes	<p>Efficacy: Primary outcome was death from any cause / cardiopulmonary death / sudden death or PE between time of randomisation and day 30. Secondary outcome was death from any cause / cardiopulmonary death / sudden death or PE between time of randomisation and day 14 and time of randomisation and day 90</p> <p>Safety: major haemorrhage, clinically relevant non-major bleeding, minor bleeding, thrombocytopaenia, heparin induced thrombocytopaenia during treatment period</p> <p>Haemorrhage definition: (major) overt bleeding associated with death, need for transfusion of at least 2 units of packed red cells or whole blood, a fall in haemoglobin of 20 g/L, requirement for major therapeutic intervention to control bleeding, a bleeding site that was retroperitoneal, intracranial or intraocular; (minor) overt bleeding that did not meet the criteria for major haemorrhage</p>
Notes	<p>Participants were also wearing elastic stocking with graduated compression</p> <p>For the purposes of this analysis, data collected at day 30 after randomisation, which corresponds with the primary outcome</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment code list of random permuted blocks were generated by an independent contract research organization and stratified according to centre. Investigators assigned patients in sequential order of treatment number available at centre
Allocation concealment (selection bias)	Low risk	Investigators assigned patients in sequential order of treatment number available at centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators and patients were unaware of treatment assignments
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Steering committee / data and safety monitoring members were unaware of treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol is available and all but one of the study's pre-specified outcomes have been reported. Thrombocytopaenia was not reported but there were no case of heparin induced thrombocytopaenia
Other bias	Unclear risk	Funding of study supported by Sanofi

MEDENOX 1999

Methods	Study design: Phase III, multi-centre, randomised, double blind trial with 3 parallel groups Intention-to-treat analysis: yes Countries: Canada and various European countries
Participants	Number: 1102 (enoxaparin 20 mg n = 364; enoxaparin 40 mg n = 367; placebo n = 371). Age: (mean years $\pm$ SD) enoxaparin 20 mg 72.9 $\pm$ 10.1; enoxaparin 40 mg 73.1 $\pm$ 10.8; placebo 74.1 $\pm$ 10.6 Sex: (M/F) enoxaparin 20 mg 187/176; enoxaparin 40 mg 171/196; placebo 192/178 Inclusion criteria: patients > 40 years, hospitalised with an acute medical illness who were not immobilised for more than 3 days Exclusion criteria: women of child-bearing age if pregnant, breast-feeding, or not using contraception; stroke or major surgery in the previous 3 months; contraindications to iodinated contrast media; serum creatinine concentration > 1.7 mg/dl; intubation; thrombophilia; HIV; uncontrolled arterial hypertension; active peptic ulcer; bacterial endocarditis; sensitivity to heparin or HIT, or platelet count < 100,000 $\times$ 10 ⁹ /L; patients requiring anticoagulation Reason for hospitalisation (n (%)): congestive heart failure NYHA class III (enoxaparin 40 mg n = 103 (28.1), enoxaparin 20 mg n = 76 (20.9), control n = 95 (25.7)); congestive heart failure NYHA class IV (enoxaparin 40 mg n = 26 (7.1), enoxaparin 20 mg n = 44 (12.1), control n = 32 (8.6)); acute respiratory failure (enoxaparin 40 mg n = 195 (53.1), enoxaparin 20 mg n = 192 (52.9), control n = 202 (54.6)); acute infectious disease (enoxaparin 40 mg n = 197 (53.7), enoxaparin 20 mg n = 194 (53.4), control n = 193 (52.2)); acute rheumatic disorder (enoxaparin 40 mg n = 28 (7.6), enoxaparin 20 mg n = 40 (11.0), control n = 32 (8.6)); inflammatory bowel disease (enoxaparin 40 mg n = 3 (0.8), enoxaparin 20 mg n = 1 (0.3), control n = 1 (0.3))
Interventions	Treatment 1: LMWH (enoxaparin) 20 mg, subcutaneous injection, once daily Treatment 2: LMWH (enoxaparin) 40 mg, subcutaneous injection, once daily Control: placebo (0.2 ml isotonic saline), subcutaneous injection, once daily Duration: 6 to 14 days
Outcomes	DVT, PE, mortality, major and minor haemorrhage, thrombocytopenia Haemorrhage definition: (major) overt bleeding associated with the need for transfusion of two or more units of packed red cells or whole blood or with a decrease in haemoglobin of 20 g/L or more from baseline, or if bleeding was retroperitoneal, intracranial or fatal; (minor) overt bleeding events not meeting the criteria for major bleeding
Notes	Venographically detected DVT or documented symptomatic DVT or PE For the purposes of this analysis data used was for days 1 to 14, which corresponds to the primary outcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Low risk	Use of a central location for randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blinded with use of a matched placebo control and prefilled syringes for treatment and placebo
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were reviewed by 2 independent committees whose members were unaware of treatment assignments

MEDENOX 1999 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data accounted for and unlikely to affect results
Selective reporting (reporting bias)	Low risk	Report includes all expected outcomes
Other bias	Unclear risk	Funding of study supported by Rhône-Poulenc (Sanofi)

PREVENT 2004

Methods	Study design: Phase III, multi-centre, randomised, double blind trial with 2 parallel groups Intention-to-treat analysis: yes Countries: Africa, Australia, Canada, Europe, Israel, Lebanon, North and South America	
Participants	Number: 3706 (Treatment n = 1856; Control n = 1850) Age: (mean years $\pm$ SD) dalteparin 68.5 (11.1); placebo 68.5 (11.7) Sex: (M/F) dalteparin 884/964; placebo 888/945 Inclusion criteria: patients $\geq$ 40 years with an acute medical illness requiring a projected hospitalisation $\geq$ 4 days and had $\leq$ 3 days of prior immobilisation Exclusion criteria: acute coronary syndrome or major surgical or invasive procedure within previous month; bacterial endocarditis; immobilised lower limb due to cast or fracture, stroke within 3 months; high risk of bleeding; platelet count $< 100,000 \times 10^9/L$; contraindication to heparin; hepatic insufficiency; pregnancy or breastfeeding; or life expectancy < 1 month Reason for hospitalisation (n (%)): acute congestive heart failure NYHA class III or IV (dalteparin n = 965 (52.2), control n = 940 (51.3)); acute respiratory failure (dalteparin n = 561 (30.4), control n = 560 (30.6)); other acute conditions (dalteparin n = 749 (40.5), control n = 781 (42.6)); infectious disease (dalteparin n = 673 (36.4), control n = 687 (37.5)); rheumatological disorder (dalteparin n = 200 (10.8), control n = 198 (10.8)); inflammatory bowel disease (dalteparin n = 10 (0.5), control n = 8 (0.4))	
Interventions	Treatment: LMWH (dalteparin) 5000 IU, subcutaneous injection, once daily Control: placebo, subcutaneous injection, once daily Duration: 14 days	
Outcomes	DVT, PE, mortality, major and minor haemorrhage, thrombocytopenia Haemorrhage definition: (major) intraocular, spinal/epidural, intracranial or retroperitoneal; if haemoglobin decreased by 20 g/L or more, if a transfusion of two or more units of blood were needed, if significant medical or surgical intervention was needed, or if fatal; (minor) all other bleeding events not fitting criteria of major bleeding	
Notes	Compression ultrasound detected proximal DVT or confirmed symptomatic DVT or PE For the purposes of this analysis outcome data measured at day 21 was used.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated

Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction) (Review)

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PREVENT 2004 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blinded with use of matched placebo control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All clinical end points were centrally adjudicated by a blinded Clinical Events Committee"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion were explained and similar between groups
Selective reporting (reporting bias)	Low risk	Report includes all expected outcomes
Other bias	Unclear risk	Funding of study supported by Pharmacia Corporation

PRIME 1996

Methods	Study design: Phase III, multi-centre, randomised, double blind trial with 2 parallel groups Intention-to-treat analysis: yes Country: Germany and Austria
Participants	<p>Number: 959 (enoxaparin n = 477; UFH n = 482) Age: (years) enoxaparin 74 ± 13; UFH 74 ± 13 Sex: (M/F) enoxaparin 183/294; UFH 178/304 Inclusion criteria: patients > 18 years; hospitalised with acute medical illness and at least one additional thromboembolic risk factor (e.g. > 60 years, malignancy, obesity, former thromboembolic event, cardiac insufficiency, paresis of the lower limbs, hemiplegia, paraplegia, or severe infection); expected immobilisation for more than half of the day-time for the whole study period (7 days) Exclusion criteria: treatment with anticoagulants, antiplatelets or NSAIDs in the preceding 7 days; regional anaesthesia; pregnancy and lactation; bleeding disorder; thrombocytopaenia < 100,000 x 10⁹/L; head trauma in the previous 6 months; haemorrhagic stroke the preceding 4 weeks; endocarditis; severe liver disease or renal insufficiency; thromboembolism; or participation in a clinical trial in the preceding 6 weeks</p> <p>Reason for hospitalisation (n (%)): cardiovascular diseases (enoxaparin n = 322 (67.5), UFH n = 340 (70.5)); endocrinologic diseases (enoxaparin n = 133 (27.9), UFH n = 145 (30.1)); respiratory diseases (enoxaparin n = 116 (24.3), UFH n = 113 (23.4)); gastrointestinal and urogenital diseases (enoxaparin n = 108 (22.6), UFH n = 105 (21.8)); central nervous diseases (enoxaparin n = 75 (15.8), UFH n = 86 (17.8)); cancer (enoxaparin n = 70 (14.7), UFH n = 62 (12.9)); bone diseases (enoxaparin n = 51 (10.8), UFH n = 59 (12.2)); skin diseases (enoxaparin n = 17 (3.5), UFH n = 15 (3.1)); other (enoxaparin n = 39 (8.2), UFH n = 43 (8.9))</p>
Interventions	<p>Treatment 1: LMWH (enoxaparin) 40 mg in 0.2 ml, subcutaneous injection, once daily, plus twice daily placebo subcutaneous injections (0.2ml isotonic mannitol solution) Treatment 2: UFH 5000 IU, subcutaneous injection, three times daily Duration: 7 days</p>
Outcomes	<p>DVT, PE, mortality, major haemorrhage</p> <p>Haemorrhage definition: (major) a decrease in haemoglobin of 20 g/L or more, a transfusion of 2 or more units of blood, intracranial or retroperitoneal bleeding; (minor) not reported</p>

PRIME 1996 (Continued)

Notes Ultrasound detected DVT before and at end of study, confirmed by venography or documented symptomatic DVT. PE confirmed by pulmonary perfusion scan, angiography or autopsy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blinded with use of a matched placebo control
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Described treatment and control populations as being similar, although concern that there are no reasons given for exclusion
Selective reporting (reporting bias)	Low risk	Report includes all expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias

THE-PRINCE 2003

Methods	<p>Study design: multi-centre, controlled, randomised, open, with 2 parallel groups</p> <p>Intention-to-treat: efficacy outcomes no; safety outcomes yes</p> <p>Country: Germany</p>
Participants	<p>Number: 665 patients (enoxaparin n = 332; UFH n = 333)</p> <p>Age: (mean years $\pm$ SD) enoxaparin 70 $\pm$ 14; UFH 70 $\pm$ 14</p> <p>Sex: (M/F) enoxaparin 160/172; UFH 183/150</p> <p>Inclusion criteria: $\geq$ 18 years old; hospitalised for severe respiratory disease or heart failure; confined to bed for more than two thirds of each day</p> <p>Exclusion criteria: advanced acquired immunodeficiency syndrome; evidence of contraindications for LMWH or UFH therapy; hypersensitivity to contrast media; severe pancreatic, hepatic or renal disease; severe arterial hypertension; intracranial bleeding or haemorrhagic stroke in preceding 6 months; ocular or CNS surgery in preceding 4 weeks; coagulation disorders; drug or alcohol abuse; acute signs of DVT/PE; gastrointestinal ulcer; immobilised for > 24 hours before enrolment; taking anticoagulants/platelet inhibitors or nonsteroidal anti-inflammatory drugs</p> <p>Reason for hospitalisation (n (%)): respiratory disease (enoxaparin n = 168 (50.6), UFH n = 164 (49.4)); heart failure (enoxaparin n = 164 (49.2), UFH n = 169 (50.8))</p>

THE-PRINCE 2003 (Continued)

Interventions	<p>Treatment 1: enoxaparin 40 mg, subcutaneous injection, once daily</p> <p>Treatment 2: UFH 5000 IU, subcutaneous injection, three times daily</p> <p>Duration: 10 ± 2 days</p>
Outcomes	<p>DVT, PE, mortality, major haemorrhage</p> <p>Haemorrhage definition: (major) intracranial or retroperitoneal, overt bleeding with either a decreased in haemoglobin of 20 g/L or more, or a transfusion of at least two units of blood; (minor) not reported</p>
Notes	<p>DVT detected by fibrin monomer/D-dimer tests and verified by venography or autopsy</p> <p>Original number of randomised participants is 668, but as the three participants that withdrew do not have an explanation of which treatment group they came from this analysis can only reliably use n = 665 (enoxaparin n = 332; UFH n = 333)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation performed separately in blocks of 6 patients for each of the 2 disease groups to guarantee a stratified enrolment, but this does not describe the method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study described as open label with no use of a matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Efficacy outcomes (low risk): blinded evaluation of efficacy endpoint by independent central reviewers</p> <p>Safety outcomes (unclear risk): blinding not indicated for safety endpoints as explicitly stated for efficacy endpoints</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Efficacy outcomes (high risk): "...more patients receiving UFH discontinued the study because of adverse effects or serious adverse events, including death."</p> <p>Safety outcomes (low risk): all participants reported for safety outcomes</p>
Selective reporting (reporting bias)	Low risk	Report includes all expected outcomes
Other bias	Unclear risk	Funding of study supported by Rhône-Poulenc (Sanofi)

ASA: acetylsalicylic acid

BMI: body mass index

CNS: central nervous system

COPD: chronic obstructive pulmonary disease

CVA: cerebrovascular accident

DVT: deep vein thrombosis

EB: elastic bandages

FUT: fibrinogen uptake test

GCS: graded compression stockings

GI: gastro-intestinal

HAT: heparin-associated thrombocytopenia
 HIT: heparin-induced thrombocytopenia
 HITTS: heparin-induced thrombotic thrombocytopenia syndrome
 HIV: human immunodeficiency virus
 IU: international units
 LMWH: low molecular weight heparin
 NSAIDs: non-steroidal anti-inflammatories
 NYHA: New York Heart Association functional classification
 PE: pulmonary embolism
 SD: standard deviation
 SEM: standard error of the mean
 UFH: unfractionated heparin
 VTE: venous thromboembolism

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

Study	Reason for exclusion
Aquino 1990	Elderly patients with an acute medical disorder, however also included patients undergoing orthopaedic rehabilitation
Cade 1982a	Virtually all medical patients with DVT had suffered a recent acute MI. DVT in comparison study found mainly in patients who had undergone recent vascular or cancer surgery
Cade 1982b	Patients from coronary care unit post-MI and patients who had recently undergone surgery as well as general medical patients
EXCLAIM	All included patients received enoxaparin and then were randomised to placebo or continued on enoxaparin
Halkin 1982	Patients randomised based on hospital number (odd or even). Patient eligibility determined after allocation to treatment arm. 411 of 669 patients (even hospital number) received heparin, 689 patients with odd number acted as control
Harenberg 1990	Included patients with acute coronary and cerebrovascular disease, unable to remove from final data analysis
HESIM	Included patients with acute coronary and cerebrovascular disease, unable to remove from final data analysis
Manciet 1990	Elderly patients with an acute medical disorder, however also included patients undergoing orthopaedic rehabilitation
Mottier 1993	10% of acute medical diseases were stroke
Poniewierski 1988	No DVT identified in either treatment group. Method used to identify DVT, thermography, not sensitive enough to detect asymptomatic DVT
PROMPT	This study of hospitalised general medical > 60 years included patients with MI and cerebrovascular disease. It was not possible to extract separate data from the analysis

DVT: deep vein thrombosis
 MI: myocardial infarction

DATA AND ANALYSES

Comparison 1. Heparin versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deep vein thrombosis	7	5511	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.25, 0.67]
2 Non-fatal pulmonary embolism	6	5485	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.20, 1.07]
3 Fatal pulmonary embolism	6	27563	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.43, 1.15]
4 Combined non-fatal and/or fatal pulmonary embolism	9	27971	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.43, 1.02]
5 All cause mortality	7	27786	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.08]
6 Major bleeding	7	13804	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [1.01, 2.71]
7 Minor bleeding	5	13434	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [1.26, 2.08]
8 Thrombocytopaenia	4	13349	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.64, 1.74]

Analysis 1.1. Comparison 1 Heparin versus placebo or no treatment, Outcome 1 Deep vein thrombosis.

Analysis 1.2. Comparison 1 Heparin versus placebo or no treatment, Outcome 2 Non-fatal pulmonary embolism.

Analysis 1.3. Comparison 1 Heparin versus placebo or no treatment, Outcome 3 Fatal pulmonary embolism.

Analysis 1.4. Comparison 1 Heparin versus placebo or no treatment, Outcome 4 Combined non-fatal and/or fatal pulmonary embolism.

Analysis 1.5. Comparison 1 Heparin versus placebo or no treatment, Outcome 5 All cause mortality.

Analysis 1.6. Comparison 1 Heparin versus placebo or no treatment, Outcome 6 Major bleeding.

Analysis 1.7. Comparison 1 Heparin versus placebo or no treatment, Outcome 7 Minor bleeding.

Analysis 1.8. Comparison 1 Heparin versus placebo or no treatment, Outcome 8 Thrombocytopenia.

Comparison 2. Low molecular weight heparin versus unfractionated heparin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deep vein thrombosis	6	5942	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.96]
2 Non-fatal pulmonary embolism	6	5942	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.42, 2.08]
3 Fatal pulmonary embolism	2	3581	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.14]
4 Combined non-fatal and/or fatal pulmonary embolism	6	5942	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.39, 1.90]
5 All cause mortality	5	5605	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.54, 1.16]
6 Major bleeding	6	5942	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.22, 0.83]
7 Minor bleeding	3	3876	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.48, 1.00]
8 Thrombocytopaenia	3	3876	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.08, 2.11]

Analysis 2.1. Comparison 2 Low molecular weight heparin versus unfractionated heparin, Outcome 1 Deep vein thrombosis.

Analysis 2.2. Comparison 2 Low molecular weight heparin versus unfractionated heparin, Outcome 2 Non-fatal pulmonary embolism.

Analysis 2.3. Comparison 2 Low molecular weight heparin versus unfractionated heparin, Outcome 3 Fatal pulmonary embolism.

Analysis 2.4. Comparison 2 Low molecular weight heparin versus unfractionated heparin, Outcome 4 Combined non-fatal and/or fatal pulmonary embolism.

Analysis 2.5. Comparison 2 Low molecular weight heparin versus unfractionated heparin, Outcome 5 All cause mortality.

Analysis 2.6. Comparison 2 Low molecular weight heparin versus unfractionated heparin, Outcome 6 Major bleeding.

Analysis 2.7. Comparison 2 Low molecular weight heparin versus unfractionated heparin, Outcome 7 Minor bleeding.

Analysis 2.8. Comparison 2 Low molecular weight heparin versus unfractionated heparin, Outcome 8 Thrombocytopaenia.

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Thrombosis] this term only	1193
#2	MeSH descriptor: [Thromboembolism] this term only	1005
#3	MeSH descriptor: [Venous Thromboembolism] this term only	315
#4	MeSH descriptor: [Venous Thrombosis] this term only	959
#5	(thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):ti,ab,kw	11970
#6	MeSH descriptor: [Pulmonary Embolism] explode all trees	874
#7	PE or DVT or VTE:ti,ab,kw	2187
#8	(vein* or ven*) near thromb*:ti,ab,kw	5096
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	13408
#10	MeSH descriptor: [Heparin] explode all trees	3993
#11	*heparin:ti,ab,kw	7122
#12	heparin*:ti,ab,kw	7394
#13	nadroparin* or fraxiparin* or enoxaparin or Clexane or klexane or lovenox or dalteparin or Fragmin or ardeparin or normiflo or tinzaparin or logiparin or Innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid:ti,ab,kw	1940

(Continued)

#14	antixarin or ardeparin* or bemiparin* or Zibor or cy 222 or embolex or mo-noembolex or parnaparin* or "rd 11885" or tedelparin or Kabi-2165 or Kabi 2165:ti,ab,kw	129
#15	(emt-966 or emt-967 or "pk-10 169" or pk-10169 or pk10169):ti,ab,kw	8
#16	(fr-860 or cy-216 or cy216 or seleparin* or tedegliparin or seleparin* or tedegli-parin*):ti,ab,kw	51
#17	kb 101 or kb101 or lomoparan or orgaran:ti,ab,kw	30
#18	parnaparin or fluxum or lohepa or lowhepa or "op 2123" or parvoparin or AVE5026:ti,ab,kw	29
#19	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18	8076
#20	#9 and #19 in Trials	3300
#21	SR-PVD	9869
#22	#20 and not #21 in Trials (Word variations have been searched)	1450

FEEDBACK

Anticoagulant feedback, 14 February 2011

Summary

Feedback received on this review, and other reviews and protocols on anticoagulants, is available on the Cochrane Editorial Unit website at <http://www.editorial-unit.cochrane.org/anticoagulants-feedback>.

Feedback May 2016

Summary

We read your review with interest and thank you for the most comprehensive analysis on this topic published to date. Your review helped enlighten us on the state of the evidence for an intervention that has been given a high level of importance in our clinical practice.

In your risk of bias assessment, you rate the PREVENT trial (1) as having low risk of attrition bias as "exclusions were explained and similar between groups". Upon review of the PREVENT trial, we do not come to the same conclusion for your risk of bias assessment, and in fact believe that this trial is at high risk of attrition bias for the following reasons:

In the PREVENT trial, 1856 patients were randomized to the dalteparin intervention. The authors specified that randomized patients who had a documented clinical endpoint or evaluable compression ultrasonography exam by day 21 would be included in the primary endpoint analysis. The authors then went on to explain that patients were excluded if they did not receive the study drug (n=8), or ultrasound examination at day 21 was not evaluable (n=155) or not performed (n=175). This leaves us with 1518 patients analyzed for the primary endpoint at day 21 out of the 1856 that were randomized.

For each endpoint listed in Table 3 of the PREVENT trial, there are a vast number of patients unaccounted for. This trend in incomplete outcome data is prevalent throughout the trial for nearly all safety and efficacy endpoints and Leizorovicz et al. have made no explanation as to why these patients were excluded from their analyses.

When comparing the event rates of combined asymptomatic and symptomatic DVT in the PREVENT trial, there are 32 fewer events in the dalteparin group when compared to placebo. In Analysis 1.1 of Heparin vs Placebo for the outcome DVT in your review, the absolute difference in number of DVTs is 60. It is important to note that there are 330 patients in the PREVENT trial which have incomplete outcome data for this endpoint thus we do not know how many of them may have had an event. The magnitude of missing information is far greater than the effect size and, in our opinion, we do not believe that we can make a definitive conclusion regarding the effect size given the amount of incomplete data from this trial alone.

In addition, your review states that there is a “borderline statistically significant” reduction in combined non-fatal and fatal PE with dalteparin when compared to placebo or no treatment [OR 0.66 (0.42-1.02)]. In the PREVENT trial, there were 97 patients with incomplete outcome data for the primary endpoint of symptomatic PE in the dalteparin group for which the authors did not provide an explanation for their exclusion. We believe it is plausible that in these 97 patients with missing outcome data, some of them may have had a PE. If just two of these 97 patients had a PE, it could be argued that the results would no longer be considered “borderline statistically significant” with an OR 0.70 (0.45-1.07).

We believe that it is important for the readers of your review to understand the limitations of this study, especially as it carries the most weight in your analysis of DVT which was the only endpoint assessed in your review that demonstrated statistical significance. In light of all of this, we suggest that your risk of bias assessment be reviewed and updated accordingly for the PREVENT trial.

In addition, we were surprised to see that you made no mention of why the LIFENOX (2) trial, one of the largest studies included in your review (N=8323), was excluded from your DVT analysis. It is odd that the LIFENOX trial did not include VTE as a primary endpoint, however it is specified in their study protocol that clinical examination for VTE was performed at hospital discharge, and at days 30 and 90. The protocol also stated that enoxaparin was discontinued in patients with “positive VTE”, thus the event rate should be known by the investigators. The published results from the trial did specify that there was clinical suspicion of VTE in 0.5% of patients in the enoxaparin group (22/4072) and 0.7% of patients in the placebo group (27/4044). It is clear that the LIFENOX study authors have data regarding VTE, however you do not make any comment about this in your review and we ask whether your authors attempted to contact the study investigators for further information. As this is one of the largest studies included in your review, we believe it would contribute a great deal to your Analysis 1.1 of Heparin vs Placebo for the outcome DVT.

Based on our assessment of the incomplete outcome data from the PREVENT trial and the exclusion of VTE data from LIFENOX, we do not believe that there is definitive evidence of a significant reduction in DVT with heparin compared to placebo in acutely ill medical patients. We suggest that your review makes note of these limitations when making your final conclusion regarding the benefits of heparin in DVT prevention in medical patients.

References:

(1) Leizorovicz A, Cohen AT, Turpie AGG, Olsson C-G, Vaitkus PT, Goldhaber SZ, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 2004; 17;110(7):874–9.

(2) Kakkar AK, Cimminiello C, Goldhaber SZ, Parakh R, Wang C, Bergmann J-F, et al. Low-molecular-weight heparin and mortality in acutely ill medical patients. *N Engl J Med* 2011; 29;365(26):2463–72.

Reply

Thank you for your feedback on our systematic review. We would first like to say that by highlighting the issues within the PREVENT and LIFENOX studies you are drawing on some of the major issues facing systematic reviews in terms of outcome reporting. We appreciate that you take a critical role on reporting biases and it is important to always be improving techniques to identify and report on these types of biases.

PREVENT

Concern: There is high loss of participants that could result in increased attrition bias and concerns with outcome analysis

In the methods section we do note other studies included had a high loss of participants and performed sensitivity analysis on those that had a loss of 20% or great. The PREVENT trial was not included in this analysis as it did not meet the cut-off (by only 1%) but it is worth discussing if we should include PREVENT in this sensitivity analysis for the upcoming update of the review.

We would also like to note the PREVENT authors were expecting a high loss, as this is unfortunately common in these trials, and found a need of at least 1471 participants to achieve 90% power to detect a difference of $\alpha=0.001$ for clinically relevant VTE and sudden death at day 21. Both study arms met these requirements.

We came to the conclusion that “exclusions were explained and similar between group” because there was similarity between drop-out rates between the treatment and control group, indicating that the drop outs were unlikely to be due to the study medication and therefore low risk of attrition bias. The Dalteparin group lost 18% of their randomised participants and the control group lost 20%.

To try to combat the issues of reporting by the authors we chose to include all randomised participants in our own analysis. As we calculated the loss rates were similar between the treatment and placebo group this was deemed appropriate. As you commented in your 5th paragraph that our analysis does not account for 330 participants (we assume you only meant the Dalteparin group) that did not have evaluable compression ultrasounds, we would argue that the control group lost a similar number so overall the loss would not change the overall findings.

It is a shame that there were so many missing participants, but this is not unique to this study alone, and is a theme with this type of trial. As for Table 3, it is confusing with the different total n values and we do agree it is worth getting in contact with the study authors to ask

about Table 3 and why some of the outcomes have less than the 1518 and 1473 of evaluable participants. This will be addressed in the next update of the review, and if we are unable to get a satisfactory answer from the study authors we will discuss re-evaluating the risk of bias of the trial. We will also plan to further discuss these issues within the review

LIFENOX

Concern: We did not include this study in DVT outcome

Response: It is explicitly stated by the study authors of LIFENOX that they had no intention to determine the effect of enoxaparin on VTE (as they believe this has been previously shown) and they are only interested in all-cause mortality, primarily at day 30, and also day 90. The authors say because of their main outcome of interest they did not screen for any asymptomatic DVT. In their protocol on ClinicalTrials.gov they only state the outcomes of interest as all-cause mortality and safety issues. In their report they do report deaths by PE, which we do include in our analysis. The report of the study does not in any place discuss DVT as an outcome separate from PE. However, we understand your interest in fully reporting the data within the study and we see where you describe the author's findings of VTE after day 90, at the bottom page 2468 and top of 2469. We do not believe this offers enough description for our analysis at this point (VTE diagnosed in 0.2% enoxaparin and 0.1% placebo by 'objective method'). They do not separate DVT from PE when using the term VTE, and we do not currently have a total VTE outcome for this comparison, so it would be inappropriate in the current analysis. We do agree that it is appropriate to determine if any further data could be included in the analysis and we will open communication with the LIFENOX authors to try to include this information in to the next update of the review. We would also have to verify how they diagnosed DVT and note they did not screen for any asymptomatic DVT.

Contributors

Feedback: Tania Alia B.Sc.(Pharm), Carolyn Wilson B.Sc.(Pharm), Aaron M. Tejani B.Sc.(Pharm), PharmD

TA: I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment

Reply: Rachel Forster and Raza Alikhan on behalf of the review authors

Feedback June 2016

Summary

We read your review with interest and thank you for investigating an important topic that is now a required organizational practice here in Canada (1). Regarding analysis 1.4, the authors arrive at the conclusion that heparin had a "borderline statistically significant" reduction in combined non-fatal and fatal PE when compared to placebo. After looking at the studies in detail, we arrive at a different conclusion for this result.

Bergmann 1996 included in analysis 1.4 was, at the time, presented as an abstract when the reviewers were meta-analyzing the data. Mahé 2005 (2) presents this data in a more recent, published report. The rates of PE used for this study in analysis 1.4 in the Cochrane review (10/1230 and 17/1244 for heparin versus placebo, respectively) implies that it represents all patients randomized (n=2474). However, in Mahé 2005 (2), the same numerators used represent only those who had autopsies (10/63 and 17/60 for heparin versus placebo, respectively, as presented in Table 2), which represents approximately half of the patients who died (n=252) and 5% of the total population randomized. We believe the numbers used in analysis 1.4 in the Cochrane review is likely an underestimate, as it remains unknown how many of the 2531 (95% of those randomized) patients that are unaccounted for had a PE.

A similar error is seen with Gardlund 1996 (3) presented in this analysis. The rates of PE entered for this study in analysis 1.4 (15/5776 and 16/5917 for heparin versus placebo, respectively) implies that it represents all patients randomized (n=11,693). However, in Gardlund 1996, the same numerators used represent only those who had necropsies (15/194 and 16/189 for heparin versus placebo, respectively, as presented in table 2), representing only 3.3% (n=383) of the population randomized (3). Therefore, similar to the aforementioned Bergmann 1996 study error, there is incomplete data for 97% (n=11,310) of randomized patients. Therefore, the rates used in analysis 1.4 in the Cochrane review for Gardlund 1996 is likely underestimated as well.

Furthermore, in Gardlund 1996, rates of PE (non-fatal and fatal) are 33/194 and 26/189 in the heparin and control groups respectively, as presented in table 2 (3). However, the numbers in the numerators used in analysis 1.4 are 15 and 16, respectively, representing only the "clinically relevant fatal pulmonary embolism" rates from table 2 in the trial despite analysis 1.4 combining non-fatal and fatal PEs (3). If one were to use the combined non-fatal and fatal PE rates from the same Table in the original study report (33 and 26 as the numerators), the result of Analysis 1.4 changes to OR 0.85 [0.59,1.23], shifting towards a non-statistically significant result.

To summarize, the trial data from Bergmann 1996 (Mahé 2005) and Gardlund 1996 presented in this Cochrane review assumes the rate of PEs is from all randomized patients (2,3). However, this rate represents those who had autopsies or necropsies, representing 3.6% (n=506) of the total population randomized in both trials. Given that these two trials contribute the most weight for this analysis (63.2%), we believe that the true rates of PE are grossly underestimated. Given the significant amount of missing and incomplete data for 96% (n=13,661) of the population in these trials combined, we do not believe there is definitive evidence for a significant reduction in combined non-fatal and fatal PE with heparin compared to placebo in acutely ill medical patients. We suggest that the review authors acknowledges these errors when making their final conclusion. We suggest the data for fatal and non-fatal PE not be analyzed until the PE rates for all randomized patients in

all studies are known. Alternatively, Analysis 1.4 should be renamed to “fatal PE occurring in patients that had autopsies” with a thorough discussion regarding the limitations/bias of such a subgroup analysis. We also suggest the phrase “borderline statistically significant” in the summary of main results section for the fatal/non-fatal PE analysis be removed so as to not mislead readers.

References

1. ROP Handbooks | Accreditation Canada [Internet]. [cited 2016 Jun 13]. Available from: <https://accreditation.ca/rop-handbooks>
2. Mahé I, Bergmann JF, d’Azémar P, Vaissie JJ, Caulin C. Lack of effect of a low-molecular-weight heparin (nadroparin) on mortality in bedridden medical in-patients: a prospective randomised double-blind study. *Eur J Clin Pharmacol*. 2005 Jul;61(5–6):347–51.
3. Group HPS, Gårdlund B. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. *The Lancet*. 1996 May 18;347(9012):1357–61.

Reply

Thank you for your clearly stated concerns with analysis 1.4 Combined non-fatal and/or fatal pulmonary embolism. You have brought up several issues that are a general concern for all systematic reviews specifically that not all studies that evaluate the same treatment comparisons will report on the same outcomes in an identical manner. It is the Cochrane Collaboration’s position to gather as much relevant data as possible and report it in a manner that is as objective as possible.

You raised a concern regarding the inclusion of Bergmann 1996 and Gardlund 1996 in the combined non-fatal and/or fatal PE outcome because they only report on fatal PE. We agree that the analysis would be far more robust if they also reported on their clinically symptomatic non-fatal PE events, but the studies simply did not collect nor report this data, which is why the outcome is an ‘and/or’ outcome. We already have separate outcomes for non-fatal PE and fatal PE separately, and combining all outcomes of a similar type is a common technique in systematic reviewing. We disagree that analysis 1.4 should be considered just ‘Fatal PE occurring in patients that had autopsies’ as this outcome includes any PE that is considered clinically symptomatic or was verified as a fatal PE, and not simply fatal PE. Of course not all included studies will have provided all outcomes we are reporting on and we can only include what they report.

As for using the fully randomised cohort as our denominator instead of just those that received autopsies, we have stated in our methods we are using an intention-to-treat model. Although only a small percentage had autopsies performed, of an already smaller percentage of participants who died, we have to make the assumption that the events identified reflect over the whole randomised population. This is a common way to get around many issues when performing a systematic review as most studies will identify and report events in many ways.

For your concern regarding the additional participants in the Gardlund 1996 study (18 additional in the heparin group and 10 additional in the control group) that were found to have a PE at autopsy, please refer to the methods section of our review which states this outcome is interested only in ‘clinically symptomatic non-fatal PE and fatal PE’. The Gardlund study does not describe whether these additional embolisms found at autopsy were clinically symptomatic, only that they were not clinically relevant fatal PE. This criteria was applied to all included studies. However, we do agree that our use of ‘borderline statistically significant’ for analysis of Combined non-fatal and/or fatal pulmonary embolism is a confusing term and we have amended throughout the text.

Contributors

Feedback: Kieran Shah and Aaron M Tejani. Affiliation: Therapeutics Initiative, University of British Columbia

KS: I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment

Reply: Rachel Forster and Raza Alikhan on behalf of the review authors

Fraisse study, 6 July 2017

Summary

I note that one of the exclusion criteria listed for this systematic review was patient admitted to Intensive Care Units (ICU). However, the study by Fraisse 2000, which was conducted in 34 ICUs in France was included in the analysis. Could you please provide an explanation for this apparent inconsistency. I note that France does have respiratory high dependency care units, which may have a difference definition to standard medical or surgical ICUs.

Reply

Thank you for your comments and bringing up this issue. At the onset of the review process we planned to include all general medical patients hospitalised with an acute illness excluding patients with stroke and myocardial infarction. It subsequently became apparent to us on reviewing studies for inclusion that a small number of published thromboprophylaxis studies in acutely ill medical patients also had surgical patients included in their analysis. These studies tended to be those where patients had been admitted to an ICU for medical care and so as it was not possible from the published results to differentiate the truly medical from the surgical patients. The Fraisse study included a clearly defined population of acutely ill medical patients (decompensated chronic obstructive pulmonary disease) and there is no question that there were no surgical patients included and therefore after discussion between review authors RA and ATC a decision was made to include the study in the analysis.

We have clarified our inclusion/exclusion criteria in the [Objectives](#) and [Methods](#) sections to specify that we included studies from intensive care units only if they clearly defined their population as medical and not post-surgical. Studies were excluded if they did not clearly define their intensive care unit population as suffering from acute medical illness.

Contributors

Feedback: Dr Greg Pearce. Affiliation: Consultant. Role: Pharmacologist

Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment? I have developed a literature based regulatory submission to support an extension of indication for fraxiparine to prevent VTE in acutely ill medical patients for a commercial client.

Reply: Raza Alikhan on behalf of the review authors

WHAT'S NEW

Date	Event	Description
15 February 2018	Feedback has been incorporated	The review authors' response to the feedback has been incorporated into the review. Minor amendments made to the review in response to the feedback.
6 July 2017	Feedback has been incorporated	Feedback received. The review authors have been invited to respond to the feedback.

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 3, 2009

Date	Event	Description
20 October 2016	Feedback has been incorporated	Review authors have responded to feedback and made amendments to the review where necessary
19 May 2016	Feedback has been incorporated	Feedback received, the review authors have been invited to respond to the feedback
12 November 2013	New search has been performed	Searches rerun, three additional studies included and one additional study excluded.
12 November 2013	New citation required but conclusions have not changed	Searches rerun, three additional studies included and one additional study excluded, full risk of bias assessments made for all included studies, data errors amended. New author has joined review team.
14 February 2011	Amended	Link to anticoagulant feedback added.
10 August 2009	Amended	Minor amendment to the text in the 'Background' section.
3 April 2009	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

RA reviewed identified studies, extracted the data, performed the analyses, and wrote the review.

RB reviewed identified studies, extracted the data and assisted in data analyses and writing of the review.

Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction) (Review)

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AC commented on the writing of the review and in previous review versions reviewed identified studies and extracted the data.

DECLARATIONS OF INTEREST

Dr Alikhan has received travel expenses to attend educational meetings from the following companies marketing parenteral anticoagulants: Aventis, Leo Pharma and Pfizer.

Dr Cohen is a medical consultant and has received consultancy and clinical trial funding from many pharmaceutical companies, including Bayer, Boehringer-Ingelheim, BMS, Daiichi, GSK, Johnson and Johnson, Mitsubishi Pharma, Pfizer, Portola, Sanofi-Aventis, Schering Plough, and Takeda. He is an advisor to the UK Government Health Select Committee, the all-party working group on thrombosis, the Department of Health, and the NHS on the prevention of VTE. He is also an advisor to Lifeblood, the thrombosis charity, and is the founder of the European educational charity the Coalition to Prevent Venous Thromboembolism. Dr Cohen is one of the principal investigators of the Medenox ([MEDENOX 1999](#)), Prevent ([PREVENT 2004](#)) and Exclaim ([EXCLAIM](#)) trials.

A member of the PVD editorial base performed data extraction and risk of bias assessment on studies where both Dr Alikhan and Dr Cohen were involved.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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

The PVD Group editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title of the review has been changed from the previous version. In the original title the term 'general medical patients' was used to describe the study population, but has been changed to 'acutely ill medical patients'. The review authors made this change because 'general medical patients' was thought to be too generic and 'acutely ill medical patients' was a more precise description, and better represents the study population used for the review.

The efficacy outcome 'symptomatic PE' was further defined as 'symptomatic non-fatal PE' and the outcome 'combined clinically symptomatic non-fatal PE and fatal PE' has been added.

Exclusion criteria regarding studies recruiting from intensive care units were clarified to specify that we excluded studies from intensive care units unless they clearly defined their population as medical and not post-surgical, as surgery increases the risk of VTE.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anticoagulants [*therapeutic use]; Heparin [*therapeutic use]; Heparin, Low-Molecular-Weight [therapeutic use]; Pulmonary Embolism [*prevention & control]; Randomized Controlled Trials as Topic; Venous Thromboembolism [*prevention & control]; Venous Thrombosis [prevention & control]

MeSH check words

Humans