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Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism (Review)

Bhutia S, Wong PF

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[Intervention Review]

Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism

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ABSTRACT

Background

In the initial treatment of venous thromboembolism (VTE) low molecular weight heparin (LMWH) is administered once or twice daily. A once daily treatment regimen is more convenient for the patient and may optimise home treatment. However, it is not clear whether a once daily treatment regimen is as safe and effective as a twice daily treatment regimen. This is the second update of a review first published in 2003.

Objectives

To compare the efficacy and safety of once daily versus twice daily administration of LMWH.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched May 2013) and CENTRAL (2013, Issue 4).

Selection criteria

Randomised clinical trials in which LMWH given once daily is compared with LMWH given twice daily for the initial treatment of VTE.

Data collection and analysis

Two review authors assessed trials for inclusion and extracted data independently.

Main results

Five studies were included with a total of 1508 participants. The pooled data showed no statistically significant difference in recurrent VTE between the two treatment regimens (OR 0.82, 0.49 to 1.39; P = 0.47). A comparison of major haemorrhagic events (OR 0.77, 0.40 to 1.45; P = 0.41), improvement of thrombus size (OR 1.41, 0.66 to 3.01; P = 0.38) and mortality (OR 1.14, 0.62 to 2.08; P = 0.68) also showed no statistically significant differences between the two treatment regimens. None of the five included studies reported data on post-thrombotic syndrome.

Authors' conclusions

Once daily treatment with LMWH is as effective and safe as twice daily treatment with LMWH.

PLAIN LANGUAGE SUMMARY

Once versus twice daily injections of low molecular weight heparin for the initial treatment of blood clots in the veins

Blood clots in the veins (venous thromboembolism (VTE)) can develop spontaneously or after surgery or bed rest. Venous thromboembolism can be life threatening if clots travel to the lungs. Blood-thinning drugs such as heparin are used to dissolve clots. Low molecular weight heparin (LMWH) can be given by injection, enabling people to leave hospital. The usual treatment is two injections a day, but once a day would be more convenient. This review included five studies with a combined total of 1508 participants. The combined data showed no statistically significant difference in recurrent VTE between the once daily and twice daily treatment regimens. A comparison of major bleeding events, improvement of the blood clot size and death also showed no statistically significant difference between the two treatment regimens. None of the five included studies reported information on post-thrombotic syndrome (ongoing swelling of the affected leg, pain, and skin changes). One daily injection with LMWH is therefore as effective and safe as twice daily injections.

BACKGROUND

Description of the condition

Venous thromboembolism (VTE) is a common disease with an annual incidence of between two and three cases per 1000 inhabitants (Anderson 1991; Nordstrom 1992). Risk factors for VTE can be acquired through trauma, surgery or periods of immobilisation (Heit 2000) or can be inherited, e.g. Factor V Leiden mutation or protein C deficiency (Bertina 1994; Heijboer 1990). The disease requires immediate anticoagulant therapy, as left untreated, VTE has a high morbidity and can be fatal.

Description of the intervention

Intravenous administration of unfractionated heparin (UFH) for approximately one week has been the standard initial treatment for VTE for decades (Hirsh 1991). A group of anticoagulants derived from the unfractionated form of heparin has become available, namely low molecular weight heparins (LMWHs). Low molecular weight heparins have pharmacokinetic advantages over UFH, including a longer half-life (the compounds remain active within the body for longer), and a more predictable anticoagulant response (the dose does not have to be adjusted continually to maintain the desired level of coagulability) (Hirsh 1992). Hence, a fixed, body-weight-adjusted dose of LMWH can be administered subcutaneously without the need for laboratory monitoring. This facilitates the initial treatment and leads to a shorter hospitalisation period for people with VTE, as treatment can take place partially or entirely at home (Erkens 2010; Koopman 1996).

How the intervention might work

In the trials that established the efficacy of LMWH for the initial treatment of VTE, LMWH was usually given twice a day (Bratt 1990; Harenberg 1997; Prandoni 1992) but there are also trials in which LMWH was administered once a day (Fiessinger 1996; Lindmarker 1994). In the past few years, head to head comparisons of once versus twice daily LMWH regimens have been performed (Charbonnier 1998; Partsch 1996).

Why it is important to do this review

A single daily injection of LMWH is more convenient for people and may optimise home treatment. In addition, the appeal on economic resources is lower in a once daily administration regimen. However, it is conceivable that twice daily LMWH results in a more stable level of anticoagulation and thus in fewer complications.

This review evaluates the relative efficacy and safety of LMWH administered once daily versus twice daily.

OBJECTIVES

To assess the relative efficacy (in terms of recurrent venous thromboembolism) and safety (i.e. major haemorrhagic events) of once daily low molecular weight heparin (LMWH) versus twice daily LMWH administration in the initial treatment of people with venous thromboembolism.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised trials with an intention-to-treat analysis were included. Quasi-randomised trials were not included. Studies were excluded if they were duplicate reports; or preliminary reports of data later presented in full; and if they were dose-finding studies, in which the efficacy and safety can be under- or overestimated; or if the difference in initial treatment was confounded by differences in concomitant medication or long-term medication.

Types of participants

People with VTE, i.e. deep vein thrombosis (DVT) or pulmonary embolism (PE) or both, confirmed by objective tests were included. The following criteria were accepted for the diagnosis of VTE:

- the suspected DVT was confirmed by either venography or compression ultrasound if venography was not feasible;
- the suspected PE was confirmed by pulmonary angiography or a high probability ventilation/perfusion lung scan;
- an associated DVT was proven by either venography or compression ultrasound.

Types of interventions

Once versus twice daily administration of a fixed dose of subcutaneous LMWH as the initial treatment for VTE. Brands, doses and duration of treatment medication were registered but were not criteria for excluding trials.

Types of outcome measures

Primary outcomes

The primary outcome measures were:

- symptomatic recurrent VTE, i.e. DVT or PE, or both during the initial treatment and during follow up;
- major haemorrhagic episodes during initial treatment or within 48 hours after treatment cessation.

A diagnosis of recurrent deep venous thrombosis was accepted if one of the following criteria was met:

- a new constant intraluminal filling defect was found which was not present on the last available venogram, or extension of the thrombus on ultrasound,
- if the venogram was not diagnostic: either an abnormal 125I-fibrinogen leg scan or abnormal impedance plethysmogram or ultrasound result that had been normal before the suspected recurrent episode (Büller 1991).

A diagnosis of pulmonary embolism was accepted if one of the following criteria was met:

- a segmental defect was found on the perfusion lung scan unmatched on the previous ventilation scan or chest roentgenogram;
- a positive pulmonary angiography or spiral computed tomography (CT);
- pulmonary embolism at autopsy.

Haemorrhagic events were considered to be major if they were intracranial, retroperitoneal, led directly to death, necessitated transfusion, warranted interruption of antithrombotic treatment or required operation. All other bleeding events were classified as minor.

Secondary outcomes

The main secondary outcome was extension of the thrombus size. In addition, where data on overall mortality and incidence of the post-thrombotic syndrome were presented, these data were evaluated as well.

Search methods for identification of studies

There were no language restrictions.

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched May 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 4, 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, 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

The reference lists of articles retrieved by electronic searches were searched for additional citations.

Data collection and analysis

Selection of trials

Two review authors (for the original review MM, CVD and for the update SB, PW) independently evaluated the eligibility and methodological quality of the trials. Disagreements were resolved through discussion and consensus.

Quality of trials

Studies were evaluated to extract information on study details including route of administration, intensity of heparin therapy, and intensity of oral anticoagulant therapy. The adequacy of concealment of allocation prior to randomisation and blinding of the outcome measurement was assessed, based indirectly on the criteria of Jadad (Jadad 1996). Trials without adequate concealment of allocation and/or without blinded outcome measurement were excluded.

For future updates of the review, where the information in the original article is not clear, we will contact the authors for clarification. To date this has not been necessary.

Data extraction

For the original review, two review authors (MM, CVD) extracted data independently. The following information was collected: patient characteristics (age, gender, co-morbidity); incidence of recurrent VTE; incidence of haemorrhagic events; incidence of thrombus size improvement; and, additionally, mortality and the incidence of a post-thrombotic syndrome. Disagreements were resolved according to the same procedure used for the selection of trials. No authors were contacted for additional information.

Statistical analysis

The following comparisons were made between once and twice daily LMWH:

- incidence of symptomatic recurrent DVT and PE during the initial treatment and during follow up;
- number of people in each group with improved venographic score;
- frequency of major haemorrhagic episodes during initial treatment;
- overall mortality at the end of follow up;
- incidence of people suffering from a post-thrombotic syndrome at the end of follow up.

An odds ratio (OR) for all outcome measurements within each study was calculated (an OR of less than one favours once daily). Subsequently, a chi-square test for statistical heterogeneity was done for each of the comparisons to assess whether differences in treatment effect over individual trials were consistent with natural variation around a constant effect (Collins 1987). Finally, the ORs were combined across studies giving weight to the number of events in each of the two treatment groups in each separate study using the Mantel-Haenszel procedure (Mantel 1959).

When unfractionated heparin (UFH) is used against placebo, the risk of recurrent VTE is reduced from 20 to 6.7 percent (relative risk reduction (RRR) 67%) (Brandjes 1992). The use of LMWH (mostly twice daily) at least maintains this benefit (upper limit of 95% CI of the OR of LMWH versus UFH = 1.01) (van den Belt 1999). Consequently, taking into account the changes of the comparator drug, LMWH twice daily, (OR below one means that once daily LMWH is better), the upper limit of the 95% CI of the primary analysis should not exceed one by more than 0.5, to show that at least 75% of the effect of LMWH twice daily is maintained.

RESULTS

Description of studies

Results of the search

For this update 18 additional citations relating to 11 studies were retrieved from the search of the Specialised Register. No additional studies were found from the CENTRAL search which were not in the Specialised Register. Five citations were considered to be not relevant for this review from reading the titles and abstracts and a further six studies (12 citations) (Bellosta 2007; Buller 2004; Cosmi 2012; Leizorovicz 2011; Narin 2008; Schellong 2010) were excluded. One citation (Holmström 1990) was an additional publication of the included study Holmström 1992.

Included studies

The five included studies (Charbonnier 1998; Holmström 1992; Merli 2001; Partsch 1996; Siegbahn 1989) incorporated a total of 1508 participants.

One of the five included studies included people with PE and DVT (Merli 2001). The other four studies included only people with DVT. The five included studies used four brands of low molecular weight heparin (LMWH) (enoxaparin, tinzaparin, dalteparin and nadroparin). The manufacturer recommends twice daily administration for nadroparin and enoxaparin. Once daily administration is recommended for tinzaparin and dalteparin. In all the included studies the same generic compounds were used in the head-to-head comparison of a once and a twice daily regimen. No authors were contacted for additional information.

Excluded studies

See (Characteristics of excluded studies).

For this update there were an additional six studies (12 citations) (Bellosta 2007; Buller 2004; Cosmi 2012; Leizorovicz 2011; Narin 2008; Schellong 2010) excluded making a total of 41 excluded studies.

Twenty-six trials did not compare once against twice daily administration of LMWH (Alhenc-Gelas 1994; Andersen 1997; Bara 1992; Beckman 2003; Belcaro 1999; Bratt 1988; Buller 2004; Fiessinger 1996; Harenberg 1990; Harenberg 1997; Holmström 1997; Hull 1997; Hull 2000a; Hull 2000b; Leroyer 1998; Lindmarker 1994; Luomanmaki 1996; Meyer 1995; Offord 2004; Pini 1994; Sandset 1990; Schellong 2010; Simonneau 1993; Simonneau 1997; Stricker 1999; Wartski 2000). Nine did not feature VTE as the initial event (Agnelli 1995; Boneu 1998; Bratt 1990; Cosmi 2012; Erikson 2002; Erikson 2003; Mismetti 1995; Petilla 2002; Turpie 2002). One study involved the use of unfractionated heparin for the first five days (Leizorovicz 2011). In three studies (Breddin 2001; Breddin 2003; Kakkar 2002), there were differences in concomitant medication whereby vitamin K antagonists were administered to participants in only one treatment group or treatment with vitamin K antagonists was started a few weeks later in one treatment group compared with the other group. One other study was excluded because it used different LMWH, with once daily versus twice daily for one month only and following that, the twice daily treatment arm reverted to once daily prophylactic dose. This makes comparing once daily versus twice daily regimens untenable as there were no results for effectiveness of the regimens at one month (Bellosta 2007). One trial was excluded as it was a retrospective study (Narin 2008).

Risk of bias in included studies

All five included studies were randomised clinical trials. Two studies had a double-blind design (Charbonnier 1998; Merli 2001). Two other studies were single blind (Holmström 1992; Siegbahn 1989). One study did not mention blinding (Partsch 1996). There were no indications from any of the studies that data were not analysed on an intention-to-treat basis. Participants were lost to follow up in only two studies. In one study, one person (0.3%) was lost to follow up in the twice daily group (Charbonnier 1998). In the other study (Merli 2001), seven participants (2.3%) from the group treated once daily were lost to follow up, and seven participants (2.2%) from the group treated twice daily were lost to follow up. There were no disagreements between the two review authors regarding the issue of internal validity.

Effects of interventions

Incidence of recurrent venous thromboembolism (VTE)

Three of the five included studies reported on the recurrence of symptomatic VTE (Charbonnier 1998; Merli 2001; Siegbahn 1989). In the smallest of these (Siegbahn 1989), no recurrent events were reported in either treatment group, hence an OR could not be calculated. In another study (Charbonnier 1998), a statistically non-significant lower incidence of recurrent VTE was shown in participants receiving LMWH once daily compared with those who received LMWH twice daily. While in the third study a lower incidence of VTE could be observed, which was also not statistically significant, in participants treated with LMWH twice daily (Merli 2001). When the results of these two studies (Charbonnier 1998; Merli 2001) were combined, 26 (4.2%) of the 624 participants treated with LMWH once daily and 33 (5.0%) of the 657 participants treated with LMWH twice daily had a recurrent thromboembolic event. Analysis of the pooled data showed no statistically significant difference in the incidence of recurrent thromboembolic events between LMWH once daily compared with LMWH twice daily (OR 0.82, 0.49 to 1.39; Analysis 1.1). Thus, the a priori determined criterion for equivalence was satisfied. The test for statistical heterogeneity was negative (P = 0.07), although borderline. Visual inspection does not give the impression of heterogeneity.

Incidence of haemorrhagic events

All the included studies reported on the occurrence of major haemorrhagic events. In one study none of the participants had a haemorrhagic event so an OR could not be calculated (Siegbahn 1989). Two studies showed a statistically non-significant lower incidence of haemorrhagic events in people treated with LMWH once daily (Charbonnier 1998; Holmström 1992). The other two studies showed a non-significant lower risk of major haemorrhage in people treated with LMWH twice daily compared with people treated once daily (Merli 2001; Partsch 1996). When data were combined it could be seen that 16 (2.2%) out of a total 742 participants in the once daily treatment groups suffered a haemorrhagic event compared with 22 (2.9%) events in the 766 participants in the twice daily treatment groups. Pooled analysis of the study results showed a non-significant lower incidence in haemorrhagic events in people treated with LMWH once daily compared with those who had a regimen of twice daily administration (OR 0.77, 0.40 to 1.45; Analysis 1.2). The statistical test for heterogeneity was negative (P = 0.63).

Extension of thrombus size

Data on change in thrombus size could be extracted from two studies (Holmström 1992; Siegbahn 1989). In the larger of these (Holmström 1992), interpretable repeat phlebography was available for only 87 of 101 participants. The number of people in whom an improvement of the thrombus size was found was not statistically significant. The thrombus size improved in 23 (54.8%) of the 42 participants treated with LMWH once daily and 23 (51.1%) of the 45 treated twice daily (OR 1.16, 0.50 to 2.69). The other study (Siegbahn 1989) reported that in the once daily group the thrombus size improved in six out of 10 participants; in the twice daily group the thrombus size improved in three out of 10 participants (OR 3.50, 0.55 to 22.30). Therefore, a combined OR could be calculated which showed no statistically significant difference between the

treatment groups (OR 1.41, 0.66 to 3.01; Analysis 1.3). The test for heterogeneity was negative (P = 0.29).

Mortality

Four studies reported data on overall mortality (Charbonnier 1998; Merli 2001; Partsch 1996; Siegbahn 1989). In the smallest study (Siegbahn 1989), the mortality in both treatment groups was zero. In another study (Charbonnier 1998), there were fewer deaths amongst the people treated with LMWH once daily, however, this difference was not statistically significant. In the two other studies (Merli 2001; Partsch 1996), a statistically non-significant lower number of deaths was observed in people who received LMWH twice daily compared with people who received LMWH once daily. Combining these results showed that 23 (3.3%) out of a total of 700 in the once daily groups and 21 (2.9%) out of a total of 721 in the twice daily groups died. A pooled analysis of the data showed that there was no statistically significant difference in mortality between people who are treated with LMWH twice daily compared with people treated with LMWH once daily (OR 1.14, 0.62 to 2.08; Analysis 1.4). The test for statistical heterogeneity on mortality was negative (P = 0.34).

Post-thrombotic syndrome

None of the five included studies reported data on post-thrombotic syndrome.

DISCUSSION

In this systematic review we assessed the relative efficacy and safety of once daily administration of low molecular weight heparin (LMWH) compared with a twice daily treatment regimen. Five studies comprising a total of 1508 participants were included. Procedures of randomisation and blinded outcome assessment assured reliable estimates of the pooled ORs (Schulz 1995). We found no statistically significant difference in efficacy with respect to recurrent thromboembolic events between the once daily and twice daily treatment regimens. The predefined criterion for equivalence was met since the confidence interval of the pooled OR for recurrence of VTE did not exceed 1.5. In fact, the upper limit of the 95% confidence interval was 1.39, which indicates that at least approximately 80% of the efficacy of the twice daily regimen was maintained by the once daily regimen. The observed clinical equivalence with regard to efficacy was accompanied by similar rates of bleeding complications with both the once and twice daily regimens. Also, mortality rates were low and similar in both groups. No data were available for the incidence of the development of post-thrombotic syndrome.

With regard to our two main outcome events, recurrent VTE and major haemorrhage, the following should be stated: although the pooled OR (OR 0.82, 0.49 to 1.39) for recurrent thromboembolic events was based on only two studies, it is likely that it is a reliable estimate since the methodological quality of these two largest studies (including 1261 of the total of 1508 participants) was high. Moreover, the two studies that evaluated the change in thrombus size confirm the absence of an important difference in efficacy (Holmström 1992; Siegbahn 1989). In Holmström's study, a relatively large number of the repeat venographs (14 out of 101) were not available. However, the numbers between the two groups (six in the twice daily and eight in the once daily) were comparable. Therefore, it is unlikely that the lack of available venographs in the analysis has biased the results. Data on the other main outcome, risk for major haemorrhagic events, could be derived from all studies. The observed OR indicates at least equal safety for the once daily regimen.

In meta-analyses of studies comparing UFH with LMWH in relation to recurrent VTE and bleeding outcomes, it appeared that LMWH is at least as effective and safe as UFH (Dolovich 2000; Erkens 2010; Gould 1999). In addition, in all three studies it was concluded that LMWH shows a statistically significant decrease in overall mortality compared with UFH. Frequency of administration was beyond the main scope of these studies. In only one of these meta-analyses a comparison was made between once daily and twice daily administration of LMWH and it was concluded that once daily administration of LMWH is as effective and safe as a twice daily treatment regimen (Dolovich 2000). This comparison was made across studies, rather than based on direct randomised comparisons. Therefore, the conclusion drawn by the authors can be potentially biased by group differences. However, the results are in agreement with our findings.

This systematic review demonstrates equivalence in efficacy and safety, in the short term, between once and twice daily administration of LMWH for VTE. It should be noted that there are no data available on the effect of dosing frequency on long-term recurrent thromboembolic events and the development of the post-thrombotic syndrome. Further research will be required to answer these clinically relevant questions definitively. However, an important difference in these outcomes seems implausible based on the short duration of the initial treatment regimens and their fully comparable efficacy at that stage.

It is questionable whether the results obtained from the small number of PE patients included in this systematic review can be extrapolated to all people with PE. However, if we consider DVT and PE as different manifestations of the same disease, VTE, we can conclude from the evidence presented in this systematic review, that a once daily treatment regimen is not significantly different - with respect to efficacy and safety - to a twice daily regimen in people treated for an first episode of DVT. Therefore, we have no reason to suppose that the recurrence risk in people with PE is increased. However, further research should be done to give more insight in the impact of different LMWH regimens in people with PE.

In the studies of Charbonnier (Charbonnier 1998) and Merli (Merli 2001), different LMWH compounds were used (nadroparin and enoxaparin, respectively). A meta-analysis (van der Heijden 2000) concluded that safety and efficacy of LMWH is comparable for different compounds of LMWH used in the initial treatment of VTE. Therefore, we believe that different LMWH compounds do not differ with respect to safety and efficacy in relation to a once or twice daily regimen. The best available evidence is presented in this systematic review but further research should be performed to elucidate whether the safety and efficacy of different LMWH compounds are comparable in a once or twice daily regimen.

AUTHORS' CONCLUSIONS

Implications for practice

This review has shown that once daily administration of LMWH for the initial treatment of venous thromboembolism is as safe and effective as a twice daily regimen. Either regimen is therefore acceptable in clinical practice.

Implications for research

Further research should be performed to investigate whether the safety and efficacy of different LMWH compounds are comparable in a once or twice daily regimen. These studies should also focus on the impact of different LMWH regimens in people with PE. A large randomised trial of at least two years' duration should be performed to determine the effects of dosing frequency on long-term sequelae of venous thromboembolism, such as the development of the post-thrombotic syndrome.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Charbonnier 1998

Methods	Study design: Randomised, multicentre, double blind trial. Method of randomisation: not stated. No. of exclusion post-randomisation: not stated. Lost to follow up: 1 (twice daily group).
Participants	Country: 70 centres in Europe. Setting: Hospital. No. of participants: 316 once daily group, 335 twice daily group. Age (mean): 59 ± 17 years once daily group; 60 ± 17 twice daily group. Gender: 56% male once daily group; 53% male twice daily group. Inclusion criteria: 18 years and older with acute symptomatic proximal DVT in popliteal vein or above documented by venography. Exclusion criteria: history of VTE within past two years; thrombosis extending into the vena cava; clinical symptoms at entry suggestive of PE; received full dose heparin treatment for more than 24h; surgery within the last 5 days; actively bleeding; either a known haemorrhagic diathesis or such a tendency detected by the initial pre-treatment coagulation tests (prothrombin ratio < 60%; platelet count = 150,000 mm^3; patient aPTT/control aPTT = 1.4 with no anticoagulant treatment). Other reasons for exclusion were uncontrolled hypertension; severe hepatic or renal failure and short life expectancy (< 6 months).
Interventions	Once daily nadroparin 20,500 (AXa IU/ml) and one injection of a placebo drug compared with twice daily nadroparin 10,250 (AXa IU/ml). Nadroparin treatment continued for at least 5 days. Warfarin therapy was initiated the same day or the day after and continued for 3 months. The warfarin dose was adjusted to maintain an INR of 2 to 3.
Outcomes	Symptomatic recurrent VTE, including symptomatic worsening or recurrence of the initial VTE; occurrence of a DVT in the contralateral leg; occurrence of symptomatic PE or death, certainly or possibly related to PE; major or minor bleeding; total mortality. Major bleeding was defined as overt and associated with either a decrease in the haemoglobin level (at least 2.0 g per 100 ml); a need for transfusion (2 or more units of blood); retroperitoneal or intracranial bleeding; or if bleeding led to the treatment being discontinued permanently.

Charbonnier 1998 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Holmström 1992

Methods	Study design: Open randomised, single blind (for outcome assessment), controlled study. Method of randomisation: not stated. No. of exclusions post-randomisation: 14 excluded from efficacy analysis for various reasons. Lost to follow up: not stated.
Participants	Country: Sweden. Setting: Hospital. No. of participants: 101; 50 once daily group, 51 twice daily group. Age (mean): 60.0 years (range 24 to 90) once daily group; 62.9 years (range 20 to 90) twice daily group. Gender: 33 M : 17 F once daily group; 24 M : 27 F twice daily group. Inclusion criteria: Patients with a first occurrence of DVT in the lower limb, confirmed with phlebography. Exclusion criteria: thrombosis extended over 2/3rds of the femoral vein; previous ipsilateral thrombosis; heparin treatment > 24 hours; pregnant; impaired coagulation; dementia; psychosis; renal insufficiency; allergy to contrast media; alcoholic.
Interventions	Prior to Fragmin an i.v. bolus of 5,000 U porcine sodium heparin (UFH) followed by a continuous infusion UFH (not exceeding 24 hours) adjusted to maintain the APTT at 2 to 3 times normal, was given. Subsequently patients received s.c. once daily Fragmin (generic name dalteparin) 200 U (anti-FXa)/kg or twice daily 100 U (anti-FXa)/kg. Administration of Fragmin was continued for at least 5 days. Patients were mobilised with compression stockings from day 2.
Outcomes	Marder Score based on phlebography, major and minor bleeding complications. The definition of major bleeding was not specified. The one instance of major bleeding that occurred was firstly characterised as rectal and subsequently as an epistaxis; the haemoglobin concentration fell from 123 to 94 g/litre, and two units of erythrocyte concentrate were administered.
Notes	Once daily treatment group included more calf vein thrombi.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Merli 2001

Methods	Study design: Randomised controlled, double blinded, international, multicentre trial. Method of randomisation: without stratification, in blocks of six according to ascending randomisation number. Numbers affixed to sealed treatment kits containing study medication. No. of exclusions post-randomisation: 34 in once daily group and 36 in twice daily group discontinued study medication but were still followed up for 3 months as per protocol. Lost to follow up: 1 'missing data' in twice daily group.
Participants	Country: 16 countries across Europe, United States of America and Australia. Setting: Hospital. No. of participants: 900; 298 in once daily group, 312 in twice daily group. (290 in third group given UFH) Age (mean): 60.7 years (range 19 to 91) in once daily group, 60.7 years (range 18 to 92) in twice daily group. Gender: 161 M : 137 F once daily group, 181 M : 131 F twice daily group. Inclusion criteria: > 18 years with a symptomatic lower-extremity DVT confirmed by venography or ultrasonography (including 287 patients with confirmed PE). Exclusion criteria: more than 24 hours of previous treatment with heparin or warfarin; need for thrombolytic therapy; known haemorrhagic risk, including active haemorrhage, active intestinal ulcerative disease, known angiodysplasia; or eye, spinal or central nervous system surgery within the previous month; renal or hepatic insufficiency; allergy to heparin, protamine, porcine products, iodine, or contrast media; history of heparin associated thrombocytopenia or heparin- or warfarin-associated skin necrosis; treatment with other investigational therapeutic agents within the previous 4 weeks; inferior vena cava interruption; known pregnancy or lactation.
Interventions	S.c. enoxaparin at fixed dosages of 1.0 mg/kg of body weight twice daily compared with 1.5 mg/kg body weight once daily and a injection with a placebo drug. Oral anticoagulation was started within 72 hours (INR 2 to 3) and continued for at least 3 months.
Outcomes	Recurrence of DVT or PE, major bleeding and mortality. Major bleeding defined as being associated with at least one of the following: a decrease in haemoglobin level of at least 20 g/litre; need for transfusion of at least two units of blood; retroperitoneal, intracranial, or intraocular bleeding; other associated serious clinical events; need for surgical or medical intervention; or death.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Partsch 1996

Methods	Study design: Randomised clinical trial (blinding not reported). Method of randomisation: not stated.

Partsch 1996 *(Continued)*

	No. of exclusions post-randomisation: not stated. Lost to follow up: not stated.
Participants	Country: Austria. Setting: Hospital. No. of participants: 140; 76 once daily group, 64 twice daily group. Age (mean): 69.13 ± 17.06 years once daily group; 72.21 ± 13.21 years twice daily group. Gender: 28 M : 48 F once daily group; 34 M : 30 F twice daily group. Inclusion criteria: Consecutive patients presented with DVT extending into the iliofemoral segment diagnosed by duplex ultrasonography. Exclusion criteria: previous fibrinolytic treatment; thrombectomy; complete bed rest for > 3 days within 36 hours of admission to hospital; been previously immobilised in other departments as a result of surgery, trauma or internal diseases because of inability to ambulate; pregnancy.
Interventions	Fragmin administered 200 IU/kg once daily or 100 IU/kg twice daily started immediately after randomisation for at least 7 days. Coumarin treatment was initiated approximately 10 days after diagnoses and continued for at least 3 months.
Outcomes	Decrease in frequency of PE as judged by the difference between the second V/Q scan and the initial baseline scan, major and minor bleeding, and mortality. The definition of major bleeding was not specified, but the one that occurred was characterised as "requiring 2 U of blood transfusion, gastrointestinal".
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Siegbahn 1989

Methods	Study design: Randomised, single blinded trial. Method of randomisation: not stated. No. of exclusions post-randomisation: not stated. Lost to follow up: not stated.
Participants	Country: Sweden and Denmark. Setting: Hospital. No. of participants: 20; 10 once daily group, 10 twice daily group. Age (mean): 65.5 years (range 48 to 75) once daily group, 63.4 years (range 49 to 77) twice daily group. Gender: 7 M : 3 F once daily group, 6 M : 4 F twice daily group. Inclusion criteria: over 21 years with a venographically confirmed episode of DVT.

Siegbahn 1989 *(Continued)*	
	Exclusion criteria: evidence of haemorraghic disorder; known hypersensitivity against heparin; systemic hypertension; renal insufficiency; a history of earlier ipsilateral DVT; surgery within the last month; history of intracranial bleeding; pregnancy; already on anticoagulant treatment.
Interventions	Once daily logiparin 150 XaI U/kg compared with twice daily logiparin 75 XaI U/kg. Patients received warfarin therapy from the first day of heparin treatment.
Outcomes	Recurrent VTE; change in thrombus size; and major bleeding. The definition of major bleeding was not specified. The change in thrombus size was depicted as a change in Marder score.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

APTT: activated partial thromboplastin time
DVT: deep vein thrombosis
INR: International Normalised Ratio
IU: international unit
i.v.: intravascular
PE: pulmonary embolism
s.c.: subcutaneous
UFH: unfractionated heparin
VTE: venous thromboembolism

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

Study	Reason for exclusion
Agnelli 1995	Trial participants did not suffer from VTE as initial event.
Alhenc-Gelas 1994	Did not compare once daily against twice daily treatment with LMWH.
Andersen 1997	Did not compare once daily against twice daily treatment with LMWH.
Bara 1992	Did not compare once daily against twice daily treatment with LMWH.
Beckman 2003	Did not compare once daily against twice daily treatment with LMWH.
Belcaro 1999	Did not compare once daily against twice daily treatment with LMWH.
Bellosta 2007	Used different LMWH, with once daily versus twice daily for one month only and following that, the twice daily treatment arm reverted to once daily prophylactic dose. This makes comparing once daily versus twice daily regimens untenable as there were no results for effectiveness of the regimens at one month.
Boneu 1998	Trial participants did not suffer from VTE as initial event.
Bratt 1988	Did not compare once daily against twice daily treatment with LMWH.
Bratt 1990	Trial participants did not suffer from VTE as initial event.

Study	Reason for exclusion
Breddin 2001	Patients treated with LMWH once daily received a vitamin K antagonist from day 21 onwards, while for those treated with LMWH twice daily, administration of vitamin K antagonists was started at day one.
Breddin 2003	Patients treated with LMWH once daily received a vitamin K antagonist from day 21 onwards, while for those treated with LMWH twice daily, administration of vitamin K antagonists was started at day one.
Buller 2004	Did not compare once daily against twice daily treatment with LMWH.
Cosmi 2012	Superficial vein thrombosis not DVT. The study compared different doses of LMWH and not once versus twice daily regimens.
Erikson 2002	Trial participants did not suffer from VTE as initial event.
Erikson 2003	Trial participants did not suffer from VTE as initial event.
Fiessinger 1996	Did not compare once daily against twice daily treatment with LMWH.
Harenberg 1990	Did not compare once daily against twice daily treatment with LMWH.
Harenberg 1997	Did not compare once daily against twice daily treatment with LMWH.
Holmström 1997	Did not compare once daily against twice daily treatment with LMWH.
Hull 1997	Did not compare once daily against twice daily treatment with LMWH.
Hull 2000a	Did not compare once daily against twice daily treatment with LMWH.
Hull 2000b	Did not compare once daily against twice daily treatment with LMWH.
Kakkar 2002	Patients treated with LMWH once daily received a vitamin K antagonist from day 21 onwards, while for those treated with LMWH twice daily, administration of vitamin K antagonists was started at day one.
Leizorovicz 2011	Did not compare once daily against twice daily treatment with LMWH. Compared once daily LMWH with twice daily heparin for acute treatment of DVT in elderly patients with renal impairment.
Leroyer 1998	Did not compare once daily against twice daily treatment with LMWH.
Lindmarker 1994	Did not compare once daily against twice daily treatment with LMWH.
Luomanmaki 1996	Did not compare once daily against twice daily treatment with LMWH.
Meyer 1995	Did not compare once daily against twice daily treatment with LMWH.
Mismetti 1995	Trial participants did not suffer from VTE as initial event.
Narin 2008	Retrospective study involving treatment of DVT in pregnant patients. Initial treatment involved unfractionated heparin for five days before starting LMWH.
Offord 2004	Did not compare once daily against twice daily treatment with LMWH.
Petilla 2002	Trial participants did not suffer from VTE as initial event.

Study	Reason for exclusion
Pini 1994	Did not compare once daily against twice daily treatment with LMWH.
Sandset 1990	Did not compare once daily against twice daily treatment with LMWH.
Schellong 2010	Did not compare once daily against twice daily treatment with LMWH.
Simonneau 1993	Did not compare once daily against twice daily treatment with LMWH.
Simonneau 1997	Did not compare once daily against twice daily treatment with LMWH.
Stricker 1999	Did not compare once daily against twice daily treatment with LMWH.
Turpie 2002	Trial participants did not suffer from VTE as initial event.
Wartski 2000	Did not compare once daily against twice daily treatment with LMWH.

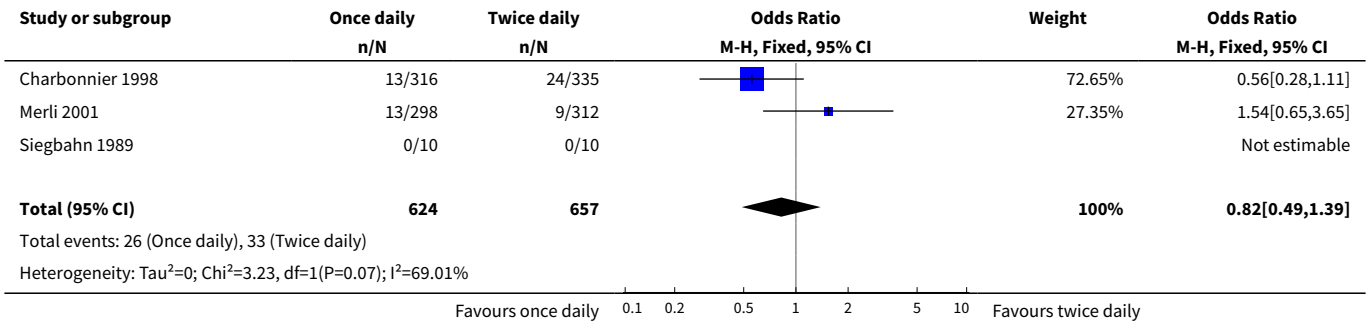
DVT: deep vein thrombosis
LMWH: low molecular weight heparin
VTE: venous thromboembolism

DATA AND ANALYSES

Comparison 1. Outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent thromboembolic events	3	1281	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.39]
2 Haemorraghic events	5	1508	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.40, 1.45]
3 Improvement of thrombus size	2	107	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.66, 3.01]
4 Mortality	4	1421	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.62, 2.08]

Analysis 1.1. Comparison 1 Outcomes, Outcome 1 Recurrent thromboembolic events.



Study or subgroup	Once daily n/N	Twice daily n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.72(P=0.47)					

Analysis 1.2. Comparison 1 Outcomes, Outcome 2 Haemorraghic events.

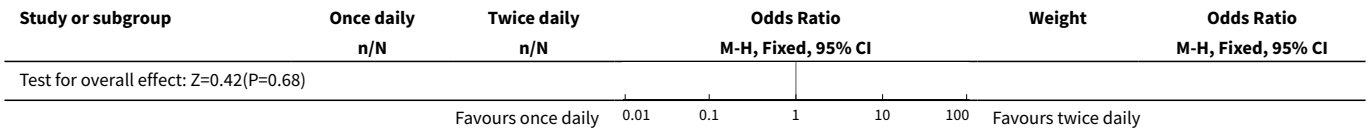
Study or subgroup	Once daily n/N	Twice daily n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Charbonnier 1998	10/316	17/335		73.35%	0.61[0.28,1.36]
Holmström 1992	0/42	1/45		6.57%	0.35[0.01,8.81]
Merli 2001	5/298	4/312		17.64%	1.31[0.35,4.94]
Partsch 1996	1/76	0/64		2.44%	2.56[0.1,64]
Siegbahn 1989	0/10	0/10			Not estimable
Total (95% CI)	**742**	**766**		**100%**	**0.77[0.4,1.45]**
Total events: 16 (Once daily), 22 (Twice daily)					
Heterogeneity: Tau^2=0; Chi^2=1.71, df=3(P=0.63); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					

Analysis 1.3. Comparison 1 Outcomes, Outcome 3 Improvement of thrombus size.

Study or subgroup	Once daily n/N	Twice daily n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Holmström 1992	23/42	23/45		89.33%	1.16[0.5,2.69]
Siegbahn 1989	6/10	3/10		10.67%	3.5[0.55,22.3]
Total (95% CI)	**52**	**55**		**100%**	**1.41[0.66,3.01]**
Total events: 29 (Once daily), 26 (Twice daily)					
Heterogeneity: Tau^2=0; Chi^2=1.14, df=1(P=0.29); I^2=11.92%					
Test for overall effect: Z=0.88(P=0.38)					

Analysis 1.4. Comparison 1 Outcomes, Outcome 4 Mortality.

Study or subgroup	Once daily n/N	Twice daily n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Charbonnier 1998	9/316	13/335		61.64%	0.73[0.31,1.72]
Merli 2001	11/298	7/312		33.12%	1.67[0.64,4.37]
Partsch 1996	3/76	1/64		5.24%	2.59[0.26,25.52]
Siegbahn 1989	0/10	0/10			Not estimable
Total (95% CI)	**700**	**721**		**100%**	**1.14[0.62,2.08]**
Total events: 23 (Once daily), 21 (Twice daily)					
Heterogeneity: Tau^2=0; Chi^2=2.15, df=2(P=0.34); I^2=6.78%					



APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Thrombosis] this term only	1176
#2	MeSH descriptor: [Thromboembolism] this term only	992
#3	MeSH descriptor: [Venous Thromboembolism] this term only	275
#4	MeSH descriptor: [Venous Thrombosis] explode all trees	2164
#5	(thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):ti,ab,kw	11677
#6	MeSH descriptor: [Pulmonary Embolism] explode all trees	857
#7	PE or DVT or VTE:ti,ab,kw	2158
#8	((vein* or ven*) near thromb*):ti,ab,kw	4960
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	13368
#10	MeSH descriptor: [Heparin] explode all trees	3959
#11	heparin*	7829
#12	UFH or UH or LMWH	1337
#13	nadroparin* or fraxiparin* or enoxaparin	1423
#14	Clexane or klexane or lovenox	81
#15	dalteparin or Fragmin or ardeparin	592
#16	normiflo or tinzaparin or logiparin	231
#17	Innohep or certoparin or sandoparin or reviparin	189
#18	clivarin* or danaproid or danaparoid	96
#19	antixarin or ardeparin* or bemiparin*	64
#20	Zibor or cy 222 or embolex or monoembolex	74
#21	parnaparin* or rd 11885 or RD1185	41

(Continued)

#22	tedelparin or Kabi-2165 or Kabi 2165	68
#23	emt-966 or emt-967 or pk-10 169 or pk-10169 or pk10169	19
#24	fr-860 or cy-216 or cy216	80
#25	seleparin* or tedegliparin or seleparin* or tedegliparin*	12
#26	wy90493 or "wy 90493"	9
#27	("kb 101" or kb101 or lomoparan or orgaran)	64
#28	parnaparin or fluxum or lohepa or lowhepa	49
#29	op 2123 or parvoparin	13
#30	ave 5026	3
#31	calciparin*	29
#32	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31	8758
#33	#9 and #32 in Trials	3324

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, 28 August 2014

Summary

My colleagues and I read with interest your Cochrane Review, "Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism." We would like to address a few points from this review.

First, we would like to acknowledge that an important outcome presented in the review is mortality. We noted that the Holmoström 1992[1] trial did not report on mortality, and was therefore not included in the mortality analysis. Because this outcome takes precedence over all others in determining if one treatment is better than another, we believe that it would be important to attain as much data on it as possible. This can be achieved by contacting the authors of the original article. Furthermore, as the odds ratio confidence interval was so wide for this outcome [(OR 1.14, 0.62 to 2.08)], it is not possible to determine whether a clinically significant difference in mortality is seen when comparing treatments. Therefore, the statement in the review that "there was a statistically non-significant difference in mortality in favour of people who are treated with LMWH twice daily compared with people treated with LMWH once daily" can be reworded to "there was a statistically non-significant difference in mortality, but a clinically significant increase or decrease cannot be ruled out." This would allow readers to put the available data into clinical context. In our opinion, the wide confidence interval for mortality limits the ability to conclude with certainty that "once daily treatment with LMWH is as effective and safe as twice daily treatment with LMWH."

We would also like to address the protocol of the review regarding the types of studies that were to be included. The protocol was to include only those that were randomized with an intention-to-treat analysis, and that had adequate allocation concealment and blinded outcome measurement. We do not believe that trials should be excluded from a systematic review due to any form of bias. Rather, biases should be outlined in the bias reports, and sensitivity analyses should be done as necessary. Regardless, based on the table of excluded studies, all reasons for exclusion appear to be reasonable. However, it should be clarified in the review that biases did not serve as exclusion criteria, which would aid in strengthening the validity of the review.

We performed a risk of bias assessment for all the included trials, and noted that missing data was present in the Merli 2001[2] trial, and that Holmström 1992[1] was not an intention-to-treat trial. Missing data is important to address, as analyses using the missing data may yield different results from those presented in the review. For example, in the Merli 2001[2] trial, 34 patients in the once daily group and 37 in the twice daily group were lost to follow-up, and no sensitivity analyses were done. Sensitivity analyses assuming hemorrhagic event worst case scenarios for patients lost to follow-up either in the once or twice daily group would yield statistically significant different results: the odds ratio would increase to 2.39 (1.45, 3.93) if assuming all lost to follow-up patients in the once daily group had hemorrhagic events, and decrease to 0.28 (0.16, 0.48) if the same is done for the twice daily group.

Thank you for conducting this review; we believe that this is an important issue, as it affects convenience, patient comfort, and cost. We hope that you consider our suggestions, and we appreciate your time.

Sincerely

Hilary Wu (BSc.Pharm), Mark Ho (BSc.Pharm), Karen Hong (BSc.Pharm), and Yin Gong (BSc.Pharm)

References
1. Holmström M, Berglund MC, Granquist S, Bratt G, Törnebohm E, Lockner D. Fragmin once or twice daily subcutaneously in the treatment of deep venous thrombosis of the leg. Thromb Res. 1992 Jul 1;67(1):49–55.
2. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med. 2001 Feb 6;134(3):191–202.

Reply

A reply from the review authors is awaited.

Contributors

Feedback: Hilary Wu, Clinical Pharmacist, Providence Health Care, Canada
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Feedback, 24 April 2015

Summary

I think we found a mistake in the table of haemorraghic events.
In the Charbonnier´s study 10 major events are reported in the once daily regimen and 17 events in the twice daily regimen. Looking at the original source, 4 events are reported in each regimen as it´s also stated in the Couturaud meta-analysis (Thromb Haemost 2001; 86: 980-4). Could you tell us if that is just a mistake or if you have other information not published.

Reply

A reply from the review authors is awaited.

Contributors

Feedback: Andres Aizman, Faculty, Pontificia Universidad Catolica de Chile
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

WHAT'S NEW

Date	Event	Description
24 April 2015	Feedback has been incorporated	Feedback was submitted for this review

HISTORY

Protocol first published: Issue 2, 2001
Review first published: Issue 1, 2003

Date	Event	Description
28 August 2014	Feedback has been incorporated	Feedback was submitted for this review
23 May 2013	New search has been performed	Searches rerun. Review was updated with six additional excluded studies.
23 May 2013	New citation required but conclusions have not changed	New authors have taken over this review. Review was updated with six additional excluded studies. Abstract and plain language summary expanded; minor copy edits made. No changes to the conclusions.
14 February 2011	Amended	Link to anticoagulant feedback added
27 October 2008	Amended	Converted to new review format.
15 May 2005	New citation required but conclusions have not changed	Review updated. No changes to the conclusions.
15 May 2005	New search has been performed	Searches re-run. Review was updated by the addition of eight new excluded studies.

CONTRIBUTIONS OF AUTHORS

2013 update:
SB and PW assessed the studies for eligibility and updated the review accordingly, and expanded the abstract and plain language summary.

2005 update and original review:
Conceiving the review: MP
Performing the review: CVD, MM
Writing the review: CVD, MM, MP
Coordinating the review: CVD

The Peripheral Vascular Diseases Review Group assisted with searching for trials.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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  The PVD Group editorial base is supported by a programme grant from the NIHR.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [*administration & dosage] [adverse effects]; Drug Administration Schedule; Hemorrhage [chemically induced]; Heparin, Low-Molecular-Weight [*administration & dosage] [adverse effects]; Pulmonary Embolism [drug therapy]; Randomized Controlled Trials as Topic; Recurrence; Thromboembolism [*drug therapy]; Venous Thrombosis [*drug therapy]

MeSH check words

Humans