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

van Dongen CJ, Mac Gillavry MR, Prins MH

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2005, Issue 3

http://www.thecochranelibrary.com

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

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>PLAIN LANGUAGE SUMMARY</td>
<td>2</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>3</td>
</tr>
<tr>
<td>METHODS</td>
<td>3</td>
</tr>
<tr>
<td>RESULTS</td>
<td>4</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>6</td>
</tr>
<tr>
<td>AUTHORS’ CONCLUSIONS</td>
<td>7</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>7</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>7</td>
</tr>
<tr>
<td>CHARACTERISTICS OF STUDIES</td>
<td>11</td>
</tr>
<tr>
<td>DATA AND ANALYSES</td>
<td>18</td>
</tr>
<tr>
<td>Analysis 1.1. Comparison 1 Outcomes, Outcome 1 Recurrent thromboembolic events.</td>
<td>18</td>
</tr>
<tr>
<td>Analysis 1.2. Comparison 1 Outcomes, Outcome 2 Haemorrhagic events.</td>
<td>19</td>
</tr>
<tr>
<td>Analysis 1.3. Comparison 1 Outcomes, Outcome 3 Mortality.</td>
<td>20</td>
</tr>
<tr>
<td>Analysis 1.4. Comparison 1 Outcomes, Outcome 4 Improvement of thrombus size.</td>
<td>20</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>21</td>
</tr>
<tr>
<td>FEEDBACK</td>
<td>21</td>
</tr>
<tr>
<td>WHAT’S NEW</td>
<td>21</td>
</tr>
<tr>
<td>HISTORY</td>
<td>21</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>22</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>22</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>22</td>
</tr>
<tr>
<td>INDEX TERMS</td>
<td>22</td>
</tr>
</tbody>
</table>
Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism

Carlo J van Dongen1, Melvin R Mac Gillavry2, Martin H Prins3

1Department of Clinical Epidemiology and Biostatistics, Room J2-204, Academic Medical Center, University of Amsterdam, 1100 DE Amsterdam, Netherlands. 2Department of Internal Medicine, Slotervaart Hospital, 1066 ED Amsterdam, Netherlands. 3Department of Epidemiology, University of Maastricht, Maastricht, Netherlands

Contact address: Carlo J van Dongen, Department of Clinical Epidemiology and Biostatistics, Room J2-204, Academic Medical Center, University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, Netherlands. c.j.vandongen@amc.uva.nl.

Editorial group: Cochrane Peripheral Vascular Diseases Group.

Publication status and date: Edited (no change to conclusions), published in Issue 3, 2011.

Review content assessed as up-to-date: 14 May 2005.


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.

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

Search methods
The Cochrane Peripheral Vascular Diseases Group searched their Trials Register (last searched April 2005), and Cochrane Central Register of Controlled Trials (CENTRAL) (last searched 2005, Issue 2). We searched MEDLINE (inception to April 2005) and EMBASE (inception to April 2005). In addition, we identified trials by handsearching relevant journals, checking cross-references and through personal communication with experts.

Selection criteria
Randomised clinical trials in which LMWH given once daily is compared with LMWH given twice daily for the initial treatment of venous thromboembolism.

Data collection and analysis
Two 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 a statistically non-significant difference in recurrent venous thromboembolism between the two treatment regimens (OR 0.82, 0.49 to 1.39). A comparison of major haemorrhagic events (OR 0.77, 0.40 to 1.45) and mortality (OR 1.14, 0.62 to 2.08) also showed a statistically non-significant difference between the two treatment regimens.
Authors’ conclusions

Once daily treatment with LMWH is as effective and safe as twice daily treatment with LMWH. However, the 95% confidence interval implies that there is a possibility that the risk of recurrent VTE might be higher when people are treated once daily. Hence, the decision to treat a person with a once daily regimen will depend on the evaluated balance between increased convenience and the potential for a lower efficacy.

PLAIN LANGUAGE SUMMARY

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

Blood clots in the veins (venous thromboembolism) 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. The review of trials found that one LMWH injection a day is apparently as safe and effective as twice daily injections. However, there is a possibility that the risk of recurrent venous thromboembolism might be higher when people are treated once daily.

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 venous thromboembolism 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 untreated venous thromboembolism 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 venous thromboembolism 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 venous thromboembolism, as treatment can take place partially or entirely at home (Koopman 1996; van den Belt 1999).

How the intervention might work

In the trials that established the efficacy of LMWH for the initial treatment of venous thromboembolism, 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; Parisch 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 venous thromboembolism, 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 venous thromboembolism:

- 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 venous thromboembolism. 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 venous thromboembolism, 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

Electronic searches

The Cochrane Peripheral Vascular Diseases (PVD) Group searched their Trials Register (last searched April 2005) and the Cochrane Central Register of Controlled Trials (CENTRAL) (last searched The Cochrane Library, 2005 Issue 2) for randomised controlled trials (RCTs) of once versus twice daily low molecular weight heparin (LMWH) for the initial treatment of venous thromboembolism. See Appendix 1 for the search strategy used to search CENTRAL.

The PVD Group has developed a Register of trials compiled from back searching and continued prospective searching of MEDLINE (from 1960 to date), EMBASE (from 1980 to date), CINAHL (1982 to date) and from handsearching journals and conference proceedings.
The full list of journals that have been handsearched, as well as the search strategies used to search databases are described in the editorial information about the Cochrane PVD Group in The Cochrane Library http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/PVD/frame.html.

We ran additional searches of MEDLINE (inception to April 2005) and EMBASE (inception to April 2005) using the following search string:

(“pulmonary embolism” OR “deep vein thrombosis” OR “venous thromboembolism”) AND (“low molecular weight heparin” OR “LMWH”) AND (“treatment” OR “therapy” OR “therapeutic”).

Searching other resources
We also checked bibliographies of relevant articles and approached colleagues directly for further trial information.

There were no restrictions for language.

Data collection and analysis

Selection of trials
Two authors (MM, CVD) independently evaluated the eligibility and methodological quality of the trials. Disagreements were resolved through discussion and consensus. When consensus could not be reached, the opinion of a third author (MP) was decisive.

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
Two authors (MM, CVD) extracted data independently. The following information was collected: patient characteristics (age, gender, co-morbidity); incidence of recurrent venous thromboembolism; 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 odds ratios 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 venous thromboembolism 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 odds ratio of LMWH versus UFH = 1.01) (van den Belt 1999). Consequently, taking into account the changes of the comparator drug, LMWH twice daily, (odds ratio 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
See: Characteristics of included studies; Characteristics of excluded studies.

Thirty-nine potentially eligible studies were identified by computerised searches of the Cochrane PVD Group’s Trials Register, CENTRAL, EMBASE and MEDLINE. One study was found by handsearching relevant journals (Siegbahn 1989).
Twenty trials did not compare once against twice daily administration of LMWH and eight did not feature venous thromboembolism as the initial event (see ‘Characteristics of excluded studies’ table and ‘Excluded studies’ section for details), and thus were excluded. Eight studies fulfilled the inclusion criteria and there were no disagreements between the two authors, however, we agreed to exclude three of these because there were differences in concomitant medication (Breddin 2001; Breddin 2003; Kakkar 2002). In these studies, 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. 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 admitted 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.

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 authors regarding the issue of internal validity.

Effects of interventions

Incidence of recurrent venous thromboembolism
Three of the five included studies reported on the recurrence of symptomatic venous thromboembolism (Charbonnier 1998; Merli 2001; Siegbahn 1989). In the smallest of these (Siegbahn 1989) no recurrent events were reported in either treatment group, hence an odds ratio could not be calculated. In another study (Charbonnier 1998) a statistically non-significant lower incidence of recurrent venous thromboembolism 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 venous thromboembolism 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 a non-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). Thus, the a priori determined criterion for equivalence was satisfied. The test for statistical heterogeneity was negative (P = 0.072), although borderline. Visual inspection does not give the impression of heterogeneity.

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 odds ratio could be calculated which showed a non-significant difference (OR 1.41, 0.66 to 3.01). The test for heterogeneity was negative (P = 0.29).

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 odds ratio 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). The statistical test for heterogeneity was negative (\(P = 0.63\)).

**Mortality**

Four studies reported data on overall mortality (Charbonnier 1998; Merli 2001; Parusch 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 significant. In the two other studies (Merli 2001; Parusch 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 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 (OR 1.14, 0.62 to 2.08). The test for statistical heterogeneity on mortality was negative (\(P = 0.21\)).

**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 odds ratios (Schulz 1995). We found a statistically non-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 odds ratio for recurrence of venous thromboembolism 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 venous thromboembolism and major haemorrhage, the following should be stated: although the pooled odds ratio (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 odds ratio indicates at least equal safety for the once daily regimen.

In meta-analyses of studies comparing UFH with LMWH in relation to recurrent venous thromboembolism and bleeding outcomes, it appeared that LMWH is at least as effective and safe as UFH (Dolovich 2000; Gould 1999; van den Belt 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 venous thromboembolism. 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 regimen 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, venous thromboembolism, 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) concludes 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.

The predefined criterion for equivalence has been met and, from that perspective, it can be concluded that there is no reason to treat people who suffer a first episode of venous thromboembolism with LMWH twice daily. However, as the confidence interval is relatively wide, the data do not justify recommendation of LMWH twice daily. However, the 95% confidence interval implies that there is a possibility that the risk of recurrent VTE might be higher when people are treated once daily. Thus, the decision to treat the patient with a once daily regimen will depend on the evaluated balance between increased convenience and the potential for a lower efficacy.

Authors’ conclusions

Implications for practice

With respect to the predefined criterion of equivalence it can be concluded from this systematic review that a once daily administration of LMWH for the initial treatment of venous thromboembolism is as safe and effective (OR 8.2, 95% CI 0.49 to 1.39) as a twice daily regimen. However, the 95% confidence interval implies that there is a possibility that the risk of recurrent VTE might be higher when people are treated once daily. Thus, the decision to treat the patient with a once daily regimen will depend on the evaluated balance between increased convenience and the potential for a lower efficacy.

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.

Acknowledgements

None.

References

References to studies included in this review

Charbonnier 1998 [published data only]

Holmström 1992 [published data only]

Merli 2001 [published data only]

Merli 2000 [published data only]

References to studies excluded from this review

Partsch 1996 [published data only]

Siegbahn 1989 [published data only]

Partsch 1996 [published data only]

Siegbahn 1989 [published data only]

Pandey 1991 [published data only]
Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism (Review)

Alhenc-Gelas 1994 [published data only]

Andersen 1997 [published data only]

Bara 1992 [published data only]

Beckman 2003 [published data only]

Belcaro 1999 [published data only]

Boneu 1998 [published data only]

Bratt 1988 [published data only]

Bratt 1990 [published data only]

Bredinin 2001 [published data only]

Bredinin 2003 [published data only]

Eriksson 2002 [published data only]

Eriksson 2003 [published data only]

Fiessinger 1996 [published data only]

Harenberg 1990 [published data only]

Harenberg 1997 [published data only]

Holmström 1997 [published data only]

Hull 1997 [published data only]

Hull 2000a [published data only]

**Hull 2000b** [published data only]


**Kakkar 2002** [published data only]


**Leroyer 1998** [published data only]


**Lindmarker 1994** [published data only]


**Luomanmaki 1996** [published data only]


**Meyer 1995** [published data only]


**Mismetti 1995** [published data only]


**Offord 2004** [published data only]


**Petilla 2002** [published data only]


**Pini 1994** [published data only]


**Sandset 1990** [published data only]


**Simonneau 1993** [published data only]


**Simonneau 1997** [published data only]


**Strickler 1999** [published data only]


**Turpie 2002** [published data only]


**Wartski 2000** [published data only]


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

Hirsh 1992


Jadad 1996


Koopman 1996


Mantel 1959


Nordstrom 1992


Prandoni 1992


Schulz 1995


van den Belt 1999


van der Heijden 2000

van der Heijden JF, Prins MH, Büller HR. For the initial treatment of venous thromboembolism: are all low molecular weight heparin compounds the same?. Thrombosis Research 2000;100(2):V121–30.

References to other published versions of this review

Van Dongen 2002

CJ van Dongen, Gillavy MR Mac, MH Prins. Once versus twice daily LMWH for the initial treatment of venous thromboembolism. Cochrane Database of Systematic Reviews
Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Characteristics of included studies  [ordered by study ID]

#### Charbonnier 1998

<table>
<thead>
<tr>
<th>Methods</th>
<th>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).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>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 &lt; 60%; platelet count = 150,000 mm3; 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 (&lt; 6 months)</td>
</tr>
<tr>
<td>Interventions</td>
<td>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</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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 100ml); a need for transfusion (2 or more units of blood); retroperitoneal or intracranial bleeding; or if bleeding led to the treatment being discontinued permanently</td>
</tr>
<tr>
<td>Notes</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
### 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 mobilized 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 characterized 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

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Partsch 1996

Methods
Study design: Randomised clinical trial (blinding not reported)
Method of randomisation: not stated.
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 immobilized in other departments as a result of surgery, trauma or internal diseases because of inability to ambulate; pregnancy
### Partsch 1996 (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>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”</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Siegbahn 1989

<table>
<thead>
<tr>
<th>Methods</th>
<th>Study design: Randomised, single blinded trial. Method of randomisation: not stated. No. of exclusions post-randomisation: not stated. Lost to follow up: not stated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>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 Exclusion criteria: evidence of haemorrhagic 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</td>
</tr>
<tr>
<td>Interventions</td>
<td>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</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
Characteristics of excluded studies  

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agnelli 1995</td>
<td>Trial participants did not suffer from VTE as initial event.</td>
</tr>
<tr>
<td>Alhenc-Gelas 1994</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Andersen 1997</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Bara 1992</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Beckman 2003</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Belcaro 1999</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Boneu 1998</td>
<td>Trial participants did not suffer from VTE as initial event.</td>
</tr>
<tr>
<td>Bratt 1988</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Bratt 1990</td>
<td>Trial participants did not suffer from VTE as initial event.</td>
</tr>
<tr>
<td>Breddin 2001</td>
<td>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</td>
</tr>
<tr>
<td>Breddin 2003</td>
<td>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</td>
</tr>
<tr>
<td>Erikson 2002</td>
<td>Trial participants did not suffer from VTE as initial event.</td>
</tr>
<tr>
<td>Erikson 2003</td>
<td>Trial participants did not suffer from VTE as initial event.</td>
</tr>
<tr>
<td>Fiessinger 1996</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Harenberg 1990</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Harenberg 1997</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Study</td>
<td>Conclusion</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Holmström 1997</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Hull 1997</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Hull 2000a</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Hull 2000b</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Kakkar 2002</td>
<td>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</td>
</tr>
<tr>
<td>Leroyer 1998</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Lindmarker 1994</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Luomanmaki 1996</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Meyer 1995</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Mismetti 1995</td>
<td>Trial participants did not suffer from VTE as initial event.</td>
</tr>
<tr>
<td>Offord 2004</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Petilla 2002</td>
<td>Trial participants did not suffer from VTE as initial event.</td>
</tr>
<tr>
<td>Pini 1994</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Sandset 1990</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Simonneau 1993</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Simonneau 1997</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Stricker 1999</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
<tr>
<td>Turpie 2002</td>
<td>Trial participants did not suffer from VTE as initial event.</td>
</tr>
<tr>
<td>Wartski 2000</td>
<td>Did not compare once daily against twice daily treatment with LMWH</td>
</tr>
</tbody>
</table>

LMWH: low molecular weight heparin
VTE: thromboembolism
### Comparison 1. Outcomes

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

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

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

**Comparison:** 1 Outcomes

**Outcome:** 1 Recurrent thromboembolic events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once daily n/N</th>
<th>Twice daily n/N</th>
<th>Odds Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charbonnier 1998</td>
<td>13/316</td>
<td>24/335</td>
<td>0.56 [0.28, 1.11]</td>
<td>72.7%</td>
<td></td>
</tr>
<tr>
<td>Merli 2001</td>
<td>13/298</td>
<td>9/312</td>
<td>1.54 [0.65, 3.65]</td>
<td>27.3%</td>
<td></td>
</tr>
<tr>
<td>Siegbahn 1989</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>624</strong></td>
<td><strong>657</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.82 [0.49, 1.39]</strong></td>
</tr>
</tbody>
</table>

Total events: 26 (Once daily), 33 (Twice daily)

Heterogeneity: Chi² = 3.23, df = 1 (P = 0.07); I² = 69%

Test for overall effect: Z = 0.72 (P = 0.47)
### Analysis 1.2. Comparison 1 Outcomes, Outcome 2 Haemorrhagic events.

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

#### Comparison: 1 Outcomes

#### Outcome: 2 Haemorrhagic events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>n/N</th>
<th>n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charbonnier 1998</td>
<td>10/316</td>
<td>17/335</td>
<td>73.3 % 0.61 [0.28, 1.36]</td>
<td>17.0 %</td>
<td></td>
</tr>
<tr>
<td>Holmström 1992</td>
<td>0/42</td>
<td>1/45</td>
<td>6.6 % 0.35 [0.01, 8.81]</td>
<td>10.0 %</td>
<td></td>
</tr>
<tr>
<td>Merli 2001</td>
<td>5/298</td>
<td>4/312</td>
<td>17.6 % 1.31 [0.35, 4.94]</td>
<td>19.0 %</td>
<td></td>
</tr>
<tr>
<td>Partsch 1996</td>
<td>1/76</td>
<td>0/64</td>
<td>2.4 % 2.56 [0.10, 64.00]</td>
<td>10.0 %</td>
<td></td>
</tr>
<tr>
<td>Siegbahn 1989</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td>10.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>742</strong></td>
<td><strong>766</strong></td>
<td><strong>100.0 % 0.77 [0.40, 1.45]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 16 (Once daily), 22 (Twice daily)
Heterogeneity: $\chi^2 = 1.71$, df = 3 ($P = 0.63$); $I^2 = 0.0$
Test for overall effect: $Z = 0.82$ ($P = 0.41$)
### Analysis 1.3. Comparison 1 Outcomes, Outcome 3 Mortality

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

Comparison: 1 Outcomes

Outcome: 3 Mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once daily n/N</th>
<th>Twice daily n/N</th>
<th>Odds Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charbonnier 1998</td>
<td>9/316</td>
<td>13/335</td>
<td>61.6 % 0.73 [0.31, 1.72]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merli 2001</td>
<td>11/298</td>
<td>7/312</td>
<td>33.1 % 1.67 [0.64, 4.37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partsch 1996</td>
<td>3/76</td>
<td>1/64</td>
<td>5.2 % 2.59 [0.26, 25.52]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siegbahn 1989</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>700</strong></td>
<td><strong>721</strong></td>
<td><strong>100.0 % 1.14 [0.62, 2.08]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 23 (Once daily), 21 (Twice daily)

Heterogeneity: Chi² = 2.15, df = 2 (P = 0.34); I² = 7%

Test for overall effect: Z = 0.42 (P = 0.68)

### Analysis 1.4. Comparison 1 Outcomes, Outcome 4 Improvement of thrombus size

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

Comparison: 1 Outcomes

Outcome: 4 Improvement of thrombus size

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once daily n/N</th>
<th>Twice daily n/N</th>
<th>Odds Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmström 1992</td>
<td>23/42</td>
<td>23/45</td>
<td>89.3 % 1.16 [0.50, 2.69]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siegbahn 1989</td>
<td>6/10</td>
<td>3/10</td>
<td>10.7 % 3.50 [0.55, 22.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>52</strong></td>
<td><strong>55</strong></td>
<td><strong>100.0 % 1.41 [0.66, 3.01]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 29 (Once daily), 26 (Twice daily)

Heterogeneity: Chi² = 1.14, df = 1 (P = 0.29); I² = 12%

Test for overall effect: Z = 0.88 (P = 0.38)
Appendix 1. CENTRAL search strategy

1) EMBOLISM-AND-THROMBOSIS*:ME
2) (DEEP and (VEIN and THROMBOSIS))
3) (VENOUS and THROMBOEMBOLISM)
4) ((#1 or #2) or #3)
5) HEPARIN-LOW-MOLECULAR-WEIGHT*:ME
6) (LOW and (MOLECULAR and (WEIGHT and HEPARIN)))
7) LMWH
8) ((#5 or #6) or #7)
9) (#4 and #8)
10) (ONCE and DAILY)
11) (TWICE and DAILY)
12) (#10 and #11)
13) (#9 and #12)

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.

WHAT'S NEW

Last assessed as up-to-date: 14 May 2005.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 February 2011</td>
<td>Amended</td>
<td>Link to anticoagulant feedback added</td>
</tr>
</tbody>
</table>

HISTORY

Protocol first published: Issue 2, 2001
Review first published: Issue 1, 2003
Date | Event | Description
--- | --- | ---
27 October 2008 | Amended | Converted to new review format.
15 May 2005 | New search has been performed | Searches re-ran. Review was updated by the addition of eight new excluded studies
15 May 2005 | New citation required but conclusions have not changed | Review updated. No changes to the conclusions.

**Contributions of Authors**

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

**Index Terms**
Medical Subject Headings (MeSH)
Anticoagulants [*administration & dosage]; Drug Administration Schedule; Hemorrhage [chemically induced]; Heparin, Low-Molecular-Weight [*administration & dosage]; Pulmonary Embolism [drug therapy]; Randomized Controlled Trials as Topic; Thromboembolism [*drug therapy]; Venous Thrombosis [*drug therapy]

MeSH check words
Humans