Chapter 3

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

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Cochrane Database Syst Rev. 2003;(1):CD003074
Abstract

Background In the initial treatment of venous thromboembolism low-molecular-weight heparin 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. The objective of this review was to compare the efficacy and safety of once daily administration to a twice daily administration of low-molecular-weight heparin.

Methods Trials were identified through the Specialised Register of the Cochrane Peripheral Vascular Diseases Group (last searched May 2001), the Cochrane Controlled Trials Register (CCTR/CENTRAL) (last searched Issue 1, 2002), by hand-searching other relevant journals, by checking cross-references and through personal communication with experts. Only randomised clinical trials in which a once daily treatment regimen with low-molecular-weight heparin is compared to a twice daily regimen in the initial treatment of patients with venous thromboembolism were selected. Two reviewers assessed trials on criteria for inclusion and extracted the data independently.

Results Five studies were included with a total of 1508 patients. The pooled data showed a statistically non-significant difference in recurrent venous thromboembolism between the two treatment regimens (odds ratio (OR) 0.82; 95% confidence interval (CI) 0.49 to 1.39). A comparison of major haemorrhagic events (OR 0.77; 95% CI 0.40 to 1.45) and mortality (OR 1.14; 95% CI 0.62 to 2.08) also showed a statistically non-significant difference between the two treatment regimens.

Conclusions Once daily treatment with low-molecular-weight heparin is as effective and safe as twice daily treatment with low-molecular-weight heparin. However, the 95% confidence interval implies that there is a possibility that the risk of recurrent venous thromboembolism might be higher when patients are treated once daily. Hence 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.
Introduction

Venous thromboembolism is a common disease with an annual incidence of between two and three cases per 1000 inhabitants.\textsuperscript{1,2} Risk factors for venous thromboembolism can be acquired through trauma, surgery or periods of immobilisation\textsuperscript{3} or can be inherited e.g. Factor V Leiden mutation or protein C deficiency.\textsuperscript{4,5} The disease requires immediate anticoagulant therapy, as untreated venous thromboembolism has a high morbidity and can be fatal. The intravenous administration of unfractionated heparin for approximately one week has been the standard initial treatment for venous thromboembolism for decades.\textsuperscript{6} Recently a new group of anticoagulants derived from the unfractionated form of heparin has become available, namely low-molecular-weight heparins. low-molecular-weight heparins have pharmacokinetic advantages over unfractionated heparin, 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).\textsuperscript{7} Hence, a fixed, body-weight-adjusted dose of low-molecular-weight heparin can be administered subcutaneously without the need for laboratory monitoring. This facilitates the initial treatment and leads to a shorter hospitalisation period for patients with venous thromboembolism, as treatment can take place partially or entirely at home.\textsuperscript{8,9}

In the trials that established the efficacy of low-molecular-weight heparin for the initial treatment of venous thromboembolism, low-molecular-weight heparin was usually given twice a day\textsuperscript{10,11,12} but there are also trials in which low-molecular-weight heparin was administered once a day.\textsuperscript{13,14} Recently, head to head comparisons of once versus twice daily low-molecular-weight heparin regimens have been performed.\textsuperscript{15,16}

A single daily injection of low-molecular-weight heparin is more convenient for patients 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 low-molecular-weight heparin results in a more stable level of anticoagulation and thus in fewer complications.

In this review the relative efficacy (in terms of recurrent venous thromboembolism) and safety (i.e. major haemorrhagic events) of once daily low-molecular-weight heparin versus twice daily low-molecular-weight heparin administration in the initial treatment of patients with venous thromboembolism is assessed.

Methods

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.

We studied patients with venous thromboembolism i.e. deep vein thrombosis and/or pulmonary embolism confirmed by objective tests. The following criteria were accepted for the diagnosis of venous thromboembolism: if the suspected deep venous thrombosis was confirmed by either venography, or compression ultrasound if venography is not feasible, or if the suspected pulmonary embolism is confirmed by pulmonary angiography, or a high probability ventilation/perfusion lung scan, or, when an associated deep vein thrombosis is proven, by either venography or compression ultrasound.

The following interventions were compared: Once versus twice daily administration of a fixed dose of subcutaneous low-molecular-weight heparin as 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
The primary outcome measures were symptomatic recurrent venous thromboembolism i.e. deep vein thrombosis and/or pulmonary embolism during the initial treatment and during follow-up; major haemorrhagic episodes during initial treatment or within 48 hours after treatment cessation; and 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.

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

a. A new constant intraluminal filling defect not present on the last available venogram, or extension of the thrombus on ultrasound,
b. 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.

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

a. A segmental defect on the perfusion lung scan unmatched on the previous ventilation scan or chest roentgenogram,
b. A positive pulmonary angiography or spiral CT,
c. 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.

**Search strategy for identification of studies**

This review has drawn on the search strategy developed for the Cochrane Peripheral Vascular Diseases Group as a whole. All publications describing (or which might describe) randomised controlled trials (RCTs) of once versus twice daily low-molecular-weight heparin for initial treatment of venous thromboembolism were sought through electronic searches of the Cochrane Peripheral Vascular Diseases Specialized Trials Register (last searched May 2001). Briefly, the Specialized Trials Register of the Group has been constructed from regular electronic searches of MEDLINE (1966 onwards), EMBASE (1980 onwards), and The Cochrane Controlled Trials Register (CCTR). Additional trials were sought through cross-referencing and personal communication with colleagues. There were no restrictions for language.

Searches of MEDLINE and EMBASE were made 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"). CCTR was last searched (Issue 1, 2002) using the following terms: 1) "embolism" AND "thrombosis" 2) ("deep" AND "vein" AND ("vein" AND "thrombosis")) 3) ("venous" AND "thromboembolism") 4) ((#1 OR #2) OR #3) 5) "heparin-low-molecular-weight" 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)

**Selection of trials**

Two reviewers (MM and CVD) evaluated the eligibility and methodological quality of the trials independently. Disagreements were resolved through discussion and consensus. When consensus could not be reached, the opinion of a third reviewer (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 binding of the outcome measurement was assessed. Trials without adequate concealment of allocation and/or without blinded outcome measurement were
excluded. When the information in articles was not clear the authors were contacted for clarification.

**Data extraction**

Data were extracted by two reviewers 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 low-molecular-weight heparin. The: (a) incidence of symptomatic recurrent deep venous thrombosis and pulmonary embolism during the initial treatment and during follow-up, (b) number of patients in each group with improved venographic score, (c) frequency of major haemorrhagic episodes during initial treatment, (d) overall mortality at the end of follow-up, (e) incidence of patients 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 (odds ratio smaller than one favours once daily). Subsequently a 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.\(^\text{18}\) 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.\(^\text{19}\)

When unfractionated heparin is used against placebo, the risk of recurrent venous thromboembolism is reduced from 20 to 6.7 percent (RRR 67\%).\(^\text{20}\) The use of low-molecular-weight heparin (mostly twice daily) at least maintains this benefit (upper limit of 95\% confidence interval (CI) of the odds ratio of low-molecular-weight heparin vs. unfractionated heparin 1.01).\(^\text{9}\) Consequently, taking into account the changes of the comparator drug, low-molecular-weight heparin twice daily, (odds ratio below one means that once daily low-molecular-weight heparin 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 low-molecular-weight heparin twice daily is maintained.

**Results**

Thirty-one potentially eligible studies were identified by computerised searches of EMBASE and MEDLINE. One study was found by hand-searching relevant
journals. Twenty-two trials did not compare once against twice daily administration and four did not feature venous thromboembolism as the initial event and thus were excluded. Six studies fulfilled the inclusion criteria and there were no disagreements between the two reviewers, however, the reviewers agreed to exclude one of these because vitamin K antagonists were administered to patients in only one treatment group. The five included studies incorporated a total of 1508 patients.

Methodological quality of included studies
All five included studies were randomised clinical trials. Two studies had a double blind design. Two other studies were single blind. One study did not mention blinding. There were no indications from any of the studies that data were not analysed on an intention to treat basis. Patients were lost to follow-up in only two studies. In one study, one patient (0.3%) was lost to follow-up in the twice daily group. In the other study, seven patients (2.3%) from the group treated once daily were lost to follow-up, and seven patients (2.2%) from the group treated twice daily were lost to follow-up. There were no disagreements between the two reviewers regarding the issue of internal validity.

One of the five included studies admitted patients with pulmonary embolism and deep vein thrombosis. The other four studies included only patients with deep vein thrombosis. The five included studies used four brands of low-molecular-weight heparin (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.

Incidence of recurrent venous thromboembolism
Three of the five included studies reported on the recurrence of symptomatic venous thromboembolism. In the smallest of these no recurrent events were reported in either treatment group, hence an odds ratio could not be calculated. In another study a statistically non-significant lower incidence of recurrent venous thromboembolism was shown in patients receiving low-molecular-weight heparin once daily compared to those who received low-molecular-weight heparin twice daily. While in the third study a lower incidence of venous thromboembolism could be observed, which was also not statistically significant, in patients treated with low-molecular-weight heparin twice daily. When the results of these two studies are combined, 26 (4.2%) of the 624 patients treated with low-molecular-weight heparin once daily and 33 (5.0%) of the 657 patients treated with low-molecular-weight heparin 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 low-molecular-weight heparin once daily compared to low-molecular-weight heparin twice daily (OR 0.82; 95% CI 0.49 to 1.39) (Figure 1). 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.

![Figure 1](image1.png)

**Figure 1** Risk of recurrent thromboembolic events at end of follow-up. Once daily treatment compared to twice daily.

### Extension of thrombus size

Data on change in thrombus size could be extracted from two studies. In the larger of these, interpretable repeat phlebography was available for only 87 of 101 patients. The number of patients 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 patients treated with low-molecular-weight heparin once daily and 23 (51.1%) of the 45 treated twice daily (OR 1.16; 95% CI 0.50 to 2.69). The other study reported that in the once daily group the thrombus-size improved in six out of 10 patients, and that in twice daily group the thrombus-size improved in three out of 10 patients (OR 3.50; 95% CI 0.55 to 22.30). Therefore a combined odds ratio could be calculated, which showed a non-significant difference (OR 1.41; 95% CI 0.66 to 3.01) (Figure 2). The test for heterogeneity was negative (p=0.29).

![Figure 2](image2.png)

**Figure 2** Change in thrombus size for a once daily and a twice daily treatment regimen.

### Incidences of haemorrhagic events

All the included studies reported on the occurrence of major haemorrhagic events. In one study none of the patients had a haemorrhagic event, so an odds ratio could not be calculated. Two studies showed a statistically non-significant lower incidence of haemorrhagic events in patients treated with low-molecular-weight heparin once daily. The other two studies showed a non-significant lower risk of major
haemorrhage in patients treated with low-molecular-weight heparin twice daily compared to patients treated once daily.\textsuperscript{15,46} When data were combined it could be seen that 16 (2.2\%) out of a total 742 patients in the once daily treatment groups suffered a haemorrhagic event compared to 22 (2.9\%) events in the 766 patients in the twice daily treatment groups. Pooled analysis of the study results showed a non-significant lower incidence in haemorrhagic events in patients treated with low-molecular-weight heparin once daily compared to those who had a regimen of twice daily administration (OR 0.77; 95\% CI 0.40 to 1.45) (Figure 3). The statistical test for heterogeneity was negative (p= 0.63).

![Figure 3](image-url) Incidence of major haemorrhagic events during initial treatment with a once daily and a twice daily treatment regimen.

**Mortality**

Four studies reported data on overall mortality.\textsuperscript{15,16,21,46} In the smallest study the mortality in both treatment groups was zero.\textsuperscript{21} In another study there were fewer deaths amongst the patients treated with low-molecular-weight heparin once daily, however this difference was not significant.\textsuperscript{16} In the two other studies a statistically non-significant lower number of deaths were observed in patients who received low-molecular-weight heparin twice daily compared to patients who received low-molecular-weight heparin once daily.\textsuperscript{15,46} 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 is a statistically non-significant difference in mortality in favour of patients who are treated with low-molecular-weight heparin twice daily compared to patients treated with low-molecular-weight heparin once daily (OR 1.14; 95\%CI 0.62 to 2.08) (Figure 4). 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 compared to a twice daily treatment regimen. Five studies comprising a total of 1508 patients were included. Procedures of randomisation and blinded outcome assessment assured reliable estimates of the pooled odds ratios.\(^\text{47}\) 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 (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 patients) was high. Moreover, the two studies that evaluated the change in thrombus-size confirm the absence of an important difference in efficacy.\(^\text{21,45}\) 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 unavailability of 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 unfractionated heparin with low-molecular-weight heparin in relation to recurrent venous thromboembolism and bleeding outcomes, it appeared that low-molecular-weight heparin is at least as effective and safe as unfractionated heparin.\textsuperscript{2,48,49} In addition, in all three studies it was concluded that low-molecular-weight heparin shows a statistically significant decrease in overall mortality compared to unfractionated heparin. 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 low-molecular-weight heparin and it was concluded that once daily administration of low-molecular-weight heparin is as effective and safe as a twice daily treatment regimen.\textsuperscript{48} 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 low-molecular-weight heparin 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 regimens and their fully comparable efficacy at that stage.

Is is questionable whether the results obtained from the small number of patients with pulmonary embolism included in this systematic review can be extrapolated to all patients with pulmonary embolism. However, if we consider deep vein thrombosis and pulmonary embolism 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 patients treated for an first episode of deep vein thrombosis. Therefore, we have no reason to suppose that the recurrence risk in patients with pulmonary embolism is increased. However, further research should be done to give more insight in the impact of different low-molecular-weight heparin regimens in patients with pulmonary embolism.

In the studies of Charbonnier and Merli, different low-molecular-weight heparin compounds were used (nadroparin and enoxaparin respectively).\textsuperscript{16,46} A recent meta-analysis concludes that safety and efficacy of low-molecular-weight heparin is comparable for different compounds of low-molecular-weight heparin used in the initial treatment of venous thromboembolism.\textsuperscript{50} Therefore we believe that different
low-molecular-weight heparin 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 the present systematic review, however, further research should be performed to elucidate whether the safety and efficacy of different low-molecular-weight heparin 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 patients who suffer a first episode of venous thromboembolism with low-molecular-weight heparin twice daily. However, as the confidence interval is relatively wide, the data do not justify recommendation of low-molecular-weight heparin once daily above a twice daily treatment regimen. Hence 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.

References


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