Do the low molecular weight heparins improve efficacy and safety of the treatment of deep venous thrombosis: a meta-analysis
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Authors' objectives
To compare the efficacy and safety of low molecular weight heparins (LMWHs) with unfractionated heparin (UFH) in the treatment of venous thromboembolism (VTE). In addition, to compare twice-daily injections of LMWH with once-daily injections.

Searching
MEDLINE was searched from January 1985 to June 1999 for publications in any language. The search terms were 'low molecular weight heparin (LMWH) and thromboembolic disease', 'LMWH and deep vein thrombosis', 'LMWH and treatment', 'LMWH and clinical trial*', 'LMWH and meta-analysis', 'LMWH and review'. In addition, Excerpta Medica and abstracts of meetings of the International Society of Thrombosis and Hemostatis were searched, and the reference lists of the reviews and trials identified were examined.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
LMWH compared with UFH. The LMWHs in the included trials were dalteparin, nadroparin, logiparin, enoxaparin, reviparin, certoparin, OP2123 and CY222; these were given either once or twice daily. LMWH and UFH were administered either intravenously or subcutaneously.

Participants included in the review
Patients with VTE, i.e. deep-vein thrombosis and/or pulmonary embolism, which was diagnosed by clinical examination or 'other objective or valid diagnostic tests'. No further information was given.

Outcomes assessed in the review
The outcomes were:
clot reduction or extension assessed by venogram, providing assessment was masked with respect to treatment assignment;
symptomatic recurrence of VTE events, i.e. deep-vein thrombosis diagnosed by venogram or ultrasound, or pulmonary embolism diagnosed by lung scan, pulmonary angiography or autopsy;
total mortality; and
major haemorrhages (fatal, requiring transfusion, leading to the interruption of treatment, or all bleeding inside the brain or into the peritoneum).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed.
**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The data extracted included: trial identification; sample size; LMWH used; route and frequency of administration; and outcomes, expressed as the number of events for the number of patients and as a percentage. The outcomes were compared by calculating the odds ratio (OR) for each outcome in the individual studies.

**Methods of synthesis**

How were the studies combined?
The ORs for the individual studies were pooled across studies, using the Mantel-Haenszel fixed-effect model (see Other Publications of Related Interest nos.1-2) to estimate a common OR and the 95% confidence intervals (CIs). The analysis was repeated using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.3). The ORs were also calculated to compare the outcomes in studies stratified according to whether LMWH was administered once or twice daily. The comparison in both groups was with UFH. The number of patients that needed to be treated was also calculated, using the incidence of events for the UFH group as the reference and applying the ORs from the meta-analysis (see Other Publications of Related Interest nos.4-5). The Schlesselmann chi-squared test was used to compare the ORs between the two strata (see Other Publications of Related Interest no.6).

How were differences between studies investigated?
The authors do not say how differences between the studies were investigated.

**Results of the review**

Twenty-one studies (4,472 participants) were included. However, not all of the studies were included in the meta-analyses.

Clot reduction (by venography).

The unadjusted overall improvement was greater in the LMWH group than in the UFH group: 443 out of 707 participants (62.7%) and 394 out of 716 participants (55%), respectively. Four studies showed a considerable improvement in clot reduction in favour of LMWH: the OR (fixed-effect model) was 0.73 (95% CI: 0.59, 0.90, p=0.004). The number that needed to switch from UFH to LMWH to get one case improvement by venography was 13 (95% CI: 8, 40).

Incidence of recurrent VTE.

There was a near to statistically significant reduction in the recurrence of VTE in favour of LMWH: the OR was 0.78 (95% CI: 0.59, 1.04, p=0.103).

Total mortality.

There was a 33% reduction in total mortality rate in favour of LMWH: the OR was 0.68 (95% CI: 0.50, 0.91, p=0.012).

Safety and haemorrhagic events.

There was a significant reduction in the risk of major haemorrhage in the LMWH group: the OR was 0.65 (95% CI: 0.43, 0.98, p=0.047). The number that needed to switch from UFH to LMWH to prevent one episode of severe bleeding was 106 (95% CI: 55, 1,294).

Comparison between LMWH administered twice daily and once daily (as compared with UFH).

The twice-daily regimen appeared to be more effective than a single dose for reducing clot size: the OR was 0.56 (95% CI: 0.42, 0.74) for two daily doses, compared with 1.08 (95% CI: 0.77, 1.51) for a single daily dose. However, the single daily dose appeared safer in terms of major bleeds: the OR was 0.07 (95% CI: 0.01, 0.54) for the once-daily dose.
and 0.79 (95% CI: 0.47, 1.32)) for the twice-daily dose.

There was no statistically-significant difference in the two regimens for the outcomes of mortality or recurrent thromboembolic events.

**Authors' conclusions**

LMWH was more effective and safer than UFH in the treatment of deep-vein thrombosis. The effects of a single dose of LMWH could be as efficient and safer than a twice-daily regimen.

**CRD commentary**

The aims of this review were clear and the search appears to have been adequate. Details of the methods used to select the studies, extract the data and assess validity, were not given. The baseline characteristics of the participants (e.g. severity of illness, age, concurrent medication) were not reported, event though the authors discussed the effect of severity of illness on the outcomes. Heterogeneity between the studies was not assessed, apart from comparing the studies in two separate groups according to the LMWH dosage regimen. No details of the lengths of follow-up were provided, either in the included studies or for the data that were pooled. There appear to be some discrepancies in the numbers of participants included in the tables, as well as arithmetical (and/or typographical) errors in the calculations of the numbers of events. The meta-analysis was appropriate despite these reservations; however, the authors' method excluded studies from the calculations where there was an event in only one arm of the trial, and this could have affected the results. The comparison between single and twice daily doses of LMWH was based on an indirect comparison, i.e. they were not compared with each other in the same trials, and is therefore unreliable.

The results of this review should be viewed with caution given the above comments.

**Implications of the review for practice and research**

**Practice:** The authors state that VTE could be treated in an out-patient setting with a daily dose of LMWH.

**Research:** The authors did not state any implications for further research.

**Bibliographic details**


**PubMedID**

10980632

**Original Paper URL**

http://www.haematologica.org/content/85/9/935.abstract

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM
MeSH
Hemorrhage /chemically induced; Heparin /standards /therapeutic use /toxicity; Heparin, Low-Molecular-Weight /standards /therapeutic use /toxicity; Humans; Phlebography; Randomized Controlled Trials as Topic; Recurrence; Survival Rate; Thromboembolism /complications /drug therapy /radiography; Venous Thrombosis /complications /drug therapy /radiography

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.