Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials


Authors' objectives
To assess the effectiveness and safety of low-molecular-weight heparins (LMWH) compared with unfractionated heparin (UFH) for treatment of acute deep vein thrombosis (DVT).

Searching
The authors searched the MEDLINE database (January 1985 to September 1997) using a search strategy developed by one investigator and a librarian (details of strategy are reported in an appendix to the review). The authors also reviewed the reference lists of retrieved articles, scanned abstracts from conference proceedings, and contacted investigators and pharmaceutical companies for additional relevant studies.

Abstracts were included only when full reports of the methods and results were supplied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) which compared subcutaneously administered low-molecular-weight heparins (LMWH) with adjusted-dose unfractionated heparin (UFH) and which randomly assigned participants to treatment groups. Studies had to use objective methods to confirm the initial episode of DVT and also in assessing one or more of the clinical outcomes. Participants had to be followed for at least 3 months and only 1 trial was double-blinded.

Dose-ranging studies and studies that permitted a change in the dose of LMWH during the trial were excluded.

Specific interventions included in the review
Low-molecular-weight heparins (LMWH) in a fixed-dose administered subcutaneously (nadroparin twice daily, tinzaparin once daily, enoxaparin twice daily, dalteparin once daily and reviparin twice daily), compared with adjusted-dose unfractionated heparin (UFH).

Participants included in the review
Participants were patients with acute lower-extremity deep venous thrombosis, with or without co-existing pulmonary embolism. The mean age of participants ranged from 47.8 to 64.9 years of age for LMWH and from 47.8 to 64.9 for UFH. The percentage of males ranged from 48-62% for both LMWH and UFH groups. Participants also included patients with distal DVT, previous venous thromboembolism, cancer, heart failure, prolonged bed rest, and recent surgery or trauma.

Outcomes assessed in the review
Mortality rates over 3 to 6 months, major bleeding complications, the prevention of thromboembolic recurrences.

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 authors performed the selection.

Assessment of study quality
Study quality was evaluated using a validated 4-item instrument developed by Schulz and colleagues (see Other Publications of Related Interest). The four criteria were: proper generation of the treatment allocation sequence; proper concealment of the allocation sequence; double-blinding; and patients lost to follow-up. Two investigators independently evaluated studies for possible inclusion and resolved any disagreements by discussion. Investigators were not blinded to journal, author, or institution.
The agreement between raters for study inclusion was evaluated using the k co-efficient for inter-rater reliability. One reviewer evaluated study quality. When details were not reported in the individual trials, the information was requested from the authors of the individual trials.

**Data extraction**

Two of the reviewers extracted the data independently.

Data were extracted for the categories of: the type of LMWH preparation studied; the timing of warfarin administration; whether UFH was administered to some participants before randomisation; whether outpatient treatment with LMWH was permitted; whether participants with concurrent pulmonary embolism were enrolled; and whether the study used objective and reproducible methods to identify and confirm clinical outcomes.

Data were also extracted for minor bleeding episodes, thrombocytopenia, the death rate from recurrent thromboembolism, and the death rate among participants with cancer.

**Methods of synthesis**

How were the studies combined?

For each outcome, the authors calculated the odds ratio (OR), absolute risk reduction, and number-needed-to-treat (NNT) with 95% confidence intervals (CIs) using fixed-effect and random-effects models.

How were differences between studies investigated?

The authors used the Mantel-Haenszel method to test for heterogeneity.

Sensitivity analyses were also performed as were tests for publication bias and the number of missing trials that would be needed to change the conclusions of the meta-analysis.

**Results of the review**

Eleven RCTs met the inclusion criteria with 3,674 participants.

Compared with UFH, LMWH reduced mortality rates over 3 to 6 months of patient follow-up (OR = 0.71, 95% CI: 0.53, 0.94; p = 0.02) which was statistically significant. The NNT was 61.

For major bleeding complications, LMWH was favoured over UFH (OR = 0.57, 95% CI: 0.33, 0.99; p = 0.047), but the absolute risk reduction was small and not statistically significant (risk reduction 0.61%, 95% CI: -0.04% to 1.26%; p = 0.07) using a fixed-effect model. Using a random-effects model produced an OR of 0.71, (95% CI: 0.40, 1.27) and absolute risk reduction of 0.66 (95% CI: -0.09, 1.41).

For preventing thromboembolic recurrences, LMWH seemed as effective as UFH (OR = 0.85, 95% CI: 0.63, 1.14; p > 0.2) however this was not statistically significant.

No statistical heterogeneity was found between studies for major bleeding, recurrent thromboembolism and mortality rates (p > 0.2 for all outcomes).

Sensitivity analysis showed that the review's findings were not altered by removing individual studies, excluding participants with distal thrombosis, including recent abstract results, or relaxing the study eligibility criteria to include studies that administered adjusted dosages. Cumulative meta-analysis showed a significant mortality advantage for LMWH by the time of the third published study.

**Cost information**

The authors state that considering the findings of the review, these agents may prove highly cost-effective for treating venous thrombosis despite their current higher price.
Authors' conclusions
Low-molecular-weight heparin treatment reduces mortality rates after acute deep venous thrombosis. These drugs seem to be as safe as unfractionated heparin with respect to major bleeding complications and appear to be as effective in preventing thromboembolic recurrences.

CRD commentary
The authors have clearly stated their research question and inclusion and exclusion criteria. The literature search is good but the authors may have missed studies published outside the United States by restricting the searches to one database. The quality of the included studies was formally assessed and the authors have also reported on how the articles were selected, and how many of the reviewers were involved in the data selection and extraction.

The data extraction is reported in tables and text and the statistical pooling was appropriate. There were tests for heterogeneity and the authors have discussed several methodological and data limitations in the review.

The authors conclusions appear to follow from the results but, as the authors acknowledge, these should be viewed with caution because of the stated methodological limitations of the included studies.

Implications of the review for practice and research
The authors state that the results of their univariate analysis of study-level factors may help to generate hypotheses for further study.

There were no stated implications for practice.

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the reliability of the review and the conclusions drawn.