Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis
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Authors' objectives
To compare the efficacy and safety of low molecular weight heparin (LMWH) and unfractionated heparin in the initial treatment of deep venous thrombosis for the reduction of recurrent thromboembolic events, death, extension of thrombus and haemorrhages.

Searching
MEDLINE and manual literature searches were performed up to December 1993. Abstracts from meetings, registries of the International Society of Thrombosis and Haemostasis, and reference lists of reviews and trials, were also examined. Colleagues, investigators and manufacturers were contacted for additional material.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with control groups treated with unfractionated heparin.

Specific interventions included in the review
LMWH and unfractionated heparin (excluding Heparinoid Org-10172).

Participants included in the review
Patients with established deep venous thrombosis, as confirmed by medical examination.

Outcomes assessed in the review
Thromboembolic events (deep venous thrombosis or pulmonary embolism), major haemorrhages, total mortality and extension of thrombus were assessed.

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
The data were included on an intention to treat basis. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
Three observers independently abstracted data, and any disagreements were resolved by consensus.

Methods of synthesis
How were the studies combined?
Various fixed-effect and random-effects meta-analyses were used. The results reported are a synthesis of the log-odds as no material difference was found between the methods. A cumulative meta-analysis was also performed by year of publication.

How were differences between studies investigated?
No statistically-significant heterogeneity was noted for any outcome. Differences according to route of administration (intravenous infusion versus subcutaneous injection), and whether laboratory tests on blood samples were used for dose
adjustment of the LMWHs, were investigated.

**Results of the review**
Sixteen RCTs involving 2,045 patients were included.

LMWH significantly reduced thrombus extension (common odds ratio 0.51, 95% confidence interval, CI: 0.32, 0.83) and gave non significant reductions in recurrence of thromboembolic events (0.66, 95% CI: 0.41, 1.07), major haemorrhages (0.65, 95% CI: 0.36, 1.16) and total mortality (0.72, 95% CI: 0.46, 1.4). No significant effects of dose adjustment or route of administration were noted. The cumulative analysis suggested that the findings were not yet stable for clinical outcomes.

**Authors’ conclusions**
LMWHs tend to have a higher benefit to risk ratio than unfractionated heparin, but these findings need confirming by suitably powered clinical trials looking at clinical rather than surrogate, e.g. thrombus time, end points.

**CRD commentary**
The review methods are rigorous and comprehensive. The study is based on a rigorous and thorough literature search. However, the trials generally have short follow-up periods, and the only significant result was found for a surrogate rather than a clinical outcome, i.e. thrombus extension. Potentially clinically-important benefits of LMWH have not been excluded.

A large clinical trial with long-term follow-up of clinical outcomes is justified. The comparisons according to route and dose are of dubious value as they were performed by indirect inter-trial comparisons; it is also unclear what statistical methods were used in these comparisons.

**Implications of the review for practice and research**
The clinical superiority of LMWH needs to be proven in a clinical trial before it replaces unfractionated heparin in the treatment of deep venous thrombosis.

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