A meta-analysis of controlled clinical trials comparing low-molecular weight heparins with unfractionated heparin in unstable angina


Authors' objectives
To conduct a meta-analysis of five randomised controlled trials (RCTs), excluding enoxaparin trials, in order to detect a statistically-significant difference between unfractionated heparin (UFH) and low molecular weight heparins (LMWHs) in people with unstable angina.

Searching
MEDLINE and EMBASE were searched using the keywords 'LMWHs', 'unstable angina', 'randomized clinical trial', 'randomized trial', and 'unstable coronary'. Other (unspecified) literature was searched. The time period over which the databases were searched was not given.

Study selection
Study designs of evaluations included in the review
RCTs were eligible for inclusion. Single-blind and double-blind trials were included.

Specific interventions included in the review
Trials of LMWHs compared with UFH were eligible for inclusion. Nadroparin, dalteparin, OP2000, and tinzaparin were compared with UFH in the included trials. Studies of enoxaparin were excluded. The dosages and routes used varied between the included trials. Aspirin and other conventional therapies were given to all the participants in all of the trials.

Participants included in the review
The participants in the included trials had unstable angina or non-Q wave myocardial infarction (MI). An inclusion criterion of the included studies was rest angina within the past 24 hours with electrocardiogram signs compatible with coronary artery disease. Participants with acute MI, ST-segment-elevation MI, planned revascularisation within the following 24 hours, a corrected cause of angina or contraindications to anticoagulation, were excluded.

Outcomes assessed in the review
The pre-specified efficacy outcomes included a composite of death, MI, recurrent angina and urgent revascularisation. The safety end point was a composite of major haemorrhage, minor haemorrhage, thrombocytopenia, allergic reaction and any other adverse event. One of the three trials that were included in the safety analysis reported bleeding as an outcome. The outcomes in the trials were assessed between days 6 and 14.

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 state that they assessed validity.

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 following data were extracted: study design; the number of patients; inclusion criteria; major exclusion criteria; outcome measures; and type and dose of study drug in each group. The odds ratio (OR) and 95% confidence interval
Methods of synthesis
How were the studies combined?
The results were pooled across studies using a meta-analysis. The pooled ORs with 95% CIs were calculated using a fixed-effect model (Mantel-Haenszel-Peto) model and a random-effects model (DerSimonian and Laird) for both the efficacy and safety outcomes (see Other Publications of Related Interest nos.1-4). The results of individual trials were presented as forest plots for each meta-analytic method and for each end point. A p-value of less than 0.05 indicated statistical significance.

How were differences between studies investigated?
A statistical test for heterogeneity was applied in the meta-analyses. A p-value of less than 0.05 indicated statistical significance.

Results of the review
Five RCTs (4,097 participants) were included. Of these, only three (3,937 participants) were included in the safety analysis.

The incidence of the composite end point of efficacy was lower with LMWHs than with UFH, but the difference was reported to be not statistically significant. The pooled OR was 0.81 (95% CI: 0.68, 0.96, p=0.07) using the fixed-effect model and 0.83 (95% CI: 0.70, 0.99, p=0.08) using the random-effects model. The result of the heterogeneity test for the efficacy end point was significant (p=0.04) by both methods. There was no difference in the safety end point during the acute phase of treatment with LMWHs or UFH; the pooled ORs were 0.78 (95% CI: 0.69, 1.26, p=0.33) and 0.82 (95% CI: 0.55, 1.26, p=0.33) using the fixed-effect and random-effects models, respectively. The heterogeneity test was not significant by either method (p not reported). Forest plots for all analyses were shown.

Cost information
The authors commented that the cost of LMWHs is three to five times higher than that of UFH.

Authors' conclusions
Treatment with LMWHs (other than enoxaparin) is as effective as that with UFH.

CRD commentary
This was a clearly written review but there was insufficient detail about the patient group, search criteria or study selection process. The authors did not report any assessment of the validity of the studies. The literature search was limited, as were the search terms, and no attempt was made to search for unpublished studies. Therefore, relevant studies might have been missed. There was limited information about the participants included in the review, e.g. neither ages nor co-morbidities were reported. This may have implications for the generalisability of the results.

The authors' stated conclusion, that efficacy failed to reach statistical significance, is not consistent with the CIs reported or the forest plots shown. The assessment of trial heterogeneity was unclear, and statistical significance was defined as a p-value of less than 0.05 rather than the usual recommended level of less than 0.1. Similar results were reported to have been obtained when using fixed-effect and random-effects models of pooling for the efficacy end point; these are inconsistent with the significant result of the heterogeneity test. Visual inspection of the forest plots suggests that there is evidence of heterogeneity for both the efficacy and safety end points. One trial that included bleeding as an outcome was not included in the safety analysis, despite the authors including bleeding as one of the safety end points. However, this may have been because there were no bleeding complications in either group.

The authors' stated conclusion, that treatment with LMWHs other than enoxaparin is as effective as UFH, could only be derived from equivalence trials, which the trials in this review were not. In view of the comments above, the authors'
conclusion with respect to the efficacy of LMWHs should be treated with caution.

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

Practice: The authors did not state any implications for practice other than that in countries where resources are limited, the decision to use LMWHs or UFH has to be made by the treating physician.

Research: The authors state that cost-effectiveness analyses need to be carried out for LMWHs versus UFH to establish their place more firmly in the management of unstable angina.

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