Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis

CRD summary
This review compared enoxaparin with unfractionated heparin in patients with acute coronary syndrome. The authors concluded that enoxaparin had a significant net clinical benefit, particularly for patients with ST-segment elevation myocardial infarction. The review had some methodological and reporting shortcomings, but included a number of very large trials, and the conclusion is probably reliable.

Authors' objectives
To compare the net clinical outcome (death, myocardial infarction (MI) or major bleeding) of the low molecular weight heparin enoxaparin with unfractionated heparin (UFH) in patients with acute coronary syndromes (ACS).

Searching
PubMed was searched, but the dates of the search were not reported. The references of prior meta-analyses and identified studies were also checked.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion. Eligible studies compared enoxaparin with UFH and enrolled patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-elevation ACS. The included studies examined both patient groups, and used a range of different doses and dosing schedules for the intervention and comparator. In the included studies, the mean ages of the patients ranged from 57 to 68 years, the majority were male (range: 64 to 84%), and a substantial minority (between 9% and 30%) had diabetes. The primary outcome of the review was net clinical events, so studies that reported death, nonfatal MI or nonfatal major bleeding by 30 days, or the closest time point available, were eligible for inclusion. The included studies employed different definitions for major bleeding.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity, although they did comment on the blinding of included trials.

Data extraction
Data on the outcomes contributory to the net clinical outcome (death, MI, major bleeding) were extracted. The definitions of major bleeding used in the studies were accepted. Where more than one event was recorded for an individual patient, only one event was recorded toward the net outcome. A composite outcome of death or MI was also calculated. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each component outcome and for the net and composite outcomes. Following the data extraction, study authors were contacted to verify the data and to obtain any missing data, in particular data on intracranial haemorrhage. Where necessary, the sponsoring pharmaceutical company was contacted in order to obtain such missing data.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were pooled in a meta-analysis using the DerSimonian and Laird random-effects model. Statistical heterogeneity was assessed using the Mantel-Haenszel method. Sensitivity analyses were conducted to investigate the impact of outliers on the pooled effect.
Results of the review
Twelve RCTs with 49,076 patients were included in the review. Six (n=27,131) assessed patients with STEMI and six (n=21,945) patients with non-ST elevation ACS. There was a small discrepancy in the total number of patients reported.

One of the STEMI trials (n=20,479) was double-blinded, as were three of the non-ST elevation ACS trials (n=7,606); the remaining trials were described as open label.

Net clinical end point (death, MI or major bleeding): there was a lower occurrence of the net clinical end point of death, MI or major bleeding, which narrowly missed statistical significance, when all trials were combined (OR 0.90, 95% CI: 0.81, 1.003, p=0.051). Significant heterogeneity was detected between trials (p=0.006) as well as between patient subgroups (p=0.005). Trials assessing patients with STEMI showed a lower incidence of the net clinical end point (OR 0.84, 95% CI: 0.73, 0.97, p=0.018), while there was no significant difference between the groups in trials of patients with non-NST elevation ACS (OR 0.97, 95% CI: 0.86, 1.09, p=0.607). In neither group was there statistically significant heterogeneity between the trials.

Composite end point (death or MI): there was a significantly lower incidence of death or MI in the enoxaparin groups when all trials were combined (OR 0.84, 95% CI: 0.76, 0.92, p<0.001).

Individual end points: mortality did not differ between the groups when all trials were combined (OR 0.94, 95% CI: 0.87, 1.02, p=0.14), but MI had a lower incidence in the enoxaparin groups (OR 0.75, 95% CI: 0.65, 0.86, p<0.001) and major bleeding was significantly more common in these enoxaparin groups (OR 1.25, 95% CI: 1.04, 1.50, p=0.019).

Individual outcomes were also reported for the STEMI and non-ST elevation ACS trial subgroups.

Authors' conclusions
Enoxaparin was associated with superior efficacy to UFH. Although bleeding was increased, this was offset by reductions in deaths and the incidence of MI. The benefit of enoxaparin was found in patients with STEMI; there was no difference in net clinical benefit between the treatments for non-ST elevation ACS patients.

CRD commentary
The review question and the inclusion criteria were clear. Only one database was searched, which makes it likely that some relevant studies were not included in the review. The authors did not report using methods designed to minimise bias and error in the selection of studies for the review or in the extraction of data. They also did not report conducting an assessment of study validity. The decision to employ meta-analysis appears appropriate and suitable subgroup and sensitivity analyses were conducted. The authors' conclusions accurately reflect the pooled results of a number of large trials but, in view of the methodological and reporting issues outlined, it is difficult to be certain of their reliability.

Implications of the review for practice and research
Practice: The authors stated that the review supports the use of enoxaparin over UFH therapy, particularly in STEMI patients.

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

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Other publications of related interest


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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.