Meta-analysis of randomized trials comparing enoxaparin versus unfractionated heparin as adjunctive therapy to fibrinolysis in ST-elevation acute myocardial infarction

Theroux P, Welsh R C

CRD summary
This review assessed the effect of using enoxaparin, a low molecular weight heparin, as an additional therapy with fibrinolytic treatment (such as streptokinase) in people with ST-segment elevation acute myocardial infarction. The authors concluded that enoxaparin was more effective than unfractionated heparin. However, the rates of major bleeding when using enoxaparin were significant.

Authors' objectives
To examine efficacy and safety data for enoxaparin as an adjunctive therapy to fibrinolysis in people with acute myocardial infarction (AMI).

Searching
MEDLINE was searched from 1985 to 2002; the search terms were given. In addition, abstracts from major international cardiology conferences (1999 to 2002) were reviewed and the reference lists from retrieved articles were checked. Pharmaceutical companies and major investigators were contacted.

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

Specific interventions included in the review
Studies that assessed the impact of enoxaparin as adjunctive therapy to fibrinolysis, as compared with control, were eligible for inclusion. The comparator in the included studies was unfractionated heparin or placebo. The fibrinolytic agents used were streptokinase, tissue plasminogen activator (t-PA), tenecteplase and anistreptase. In one study some participants also received abciximab. Where stated, the average time from the onset of symptoms to drug ranged from 2.6 hours (median) to 3.899 hours (mean).

Participants included in the review
Studies on patients with ST-segment elevation AMI were eligible for inclusion. In the included studies, the mean ages of the patients ranged from 60.2 to 62.9 years and the percentage of women ranged from 18 to 27%. Some participants also had hypertension, diabetes, previous myocardial infarction, previous coronary artery bypass graft, or coronary angioplasty.

Outcomes assessed in the review
The inclusion criteria stated that studies had to report on death or AMI. Other outcomes reported included refractory ischaemia or angina, early and late patency (assessed by angiography) and bleeding complications (including major, minor and intracranial). The combined end points of death and AMI, and of death, AMI and refractory ischaemia or angina were also reported. Early patency was characterised as angiography less than 120 minutes, while late patency was defined as more than 24 hours. The Thrombolysis in Myocardial Infarction (TIMI) definition of major bleeding was used; when this was not possible, the authors stated that they used the trial definition.

How were decisions on the relevance of primary studies made?
Two investigators independently selected the studies.

Assessment of study quality
The authors did not state that they assessed validity.

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

The extracted data included baseline characteristics of the participants, details of the study design, and the numbers of events (and percentages) for each outcome in each study. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all outcomes in the individual studies. Where data for a given outcome were not available, trialists were contacted.

Methods of synthesis
How were the studies combined?
The results for each outcome were combined in a meta-analysis using Cochran's method. Pooled ORs and 95% CIs were calculated. Statistical significance was set as a P-value of less than 0.05.

How were differences between studies investigated?
The P-value of the Cochran Q chi-squared test of heterogeneity was calculated for each outcome event. Subgroup analyses were carried out, by grouping studies that used streptokinase versus those that used tenecteplase or t-PA. In one study, 66% of the patients were treated with streptokinase and the rest with anistreptase or t-PA; however, all the participants were considered to have had streptokinase in the review. For the outcome of major bleeding, the analysis was also carried out excluding the one study that used placebo.

Results of the review
Six RCTs (6,069 patients) were included. Three trials used streptokinase, two used tenecteplase, and one used t-PA as the thrombolytic agent.

There was a non significant reduction in mortality in patients treated with enoxaparin compared with control (OR 0.86, 95% CI: 0.69, 1.09, P=0.19).

Treatment with enoxaparin reduced the rates of AMI (5 studies, OR 0.58, 95% CI: 0.44, 0.75, P=<0.001), refractory ischaemia or angina (3 studies, OR 0.69, 95% CI: 0.54, 0.88, P=0.003), and the combined end points (refractory ischaemia, death or AMI: OR 0.68, 95% CI: 0.58, 0.80, P=<0.001; death or AMI: OR 0.73, 95% CI: 0.61, 0.87, P=<0.001).

There was a significant increase in minor bleeding with enoxaparin (OR 1.29, 95% CI: 1.12, 1.41, P=<0.001). The overall results for major bleeding showed a trend towards increased risk with enoxaparin (OR 1.36, 95% CI: 0.98, 1.88, P=0.06) and no significant difference for intracranial bleeding (OR 0.97, 95% CI: 0.54, 1.73, P=0.92). When one trial that used placebo as control was excluded, the OR for major bleeding was 1.34 (95% CI: 0.97, 1.87, P=0.08). Major bleeding was more frequent with t-PA or tenecteplase than with streptokinase (OR 1.44, P=0.032).

Angiographic outcomes (3 trials) showed no significant difference in early TIMI grade 2 and 3 flow between the enoxaparin and control groups. However, there was a significant improvement in flow during late angiography (TIMI grade 2-3, OR 1.90, 95% CI: 1.35, 2.68, P<0.001).

Apart from bleeding outcomes, there was little difference between outcomes when the trials were grouped by those that used t-PA and tenecteplase versus those that used streptokinase. The other results were reported in the paper.

Except for angiography late TIMI 2-3 (P=0.06), tests for analyses showed no significant heterogeneity.

Authors' conclusions
Enoxaparin is more effective than unfractionated heparin as an adjunctive therapy to thrombolytic treatment in patients
with ST-segment elevation AMI. However, the rates of major bleeding were significant when using enoxaparin, specifically with tenecteplase or t-PA.

**CRD commentary**
This is a brief report of a review. The inclusion criteria were stated. The database search was restricted to MEDLINE and the terms described seem limited; it is possible that other studies would have been identified if databases such as EMBASE or the Cochrane Library were searched. The methods of the review were not described. Subjective decisions made during the review process might have introduced bias into the results of the review. Details of the included studies, and of their individual results, were presented. The meta-analysis appears to have been appropriate.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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