Adjunctive low molecular weight heparin during fibrinolytic therapy in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized control trials

Singh S, Bahekar A, Molnar J, Khosla S, Arora R

CRD summary
The review evaluated low-molecular weight heparins versus unfractionated heparin, in addition to fibrinolytic therapy, in patients with acute ST-segment elevation myocardial infarction. Low-molecular weight heparins significantly reduced reinfarction, but increased major bleeding risk compared with unfractionated heparin. The reliability of the authors' conclusions is unclear given limitations in reporting, particularly of the review process.

Authors' objectives
To evaluate cardiac outcomes and the risk of major bleeding with low-molecular weight heparins versus unfractionated heparin as an adjunct to fibrinolytic therapy in patients with acute ST-segment elevation myocardial infarction.

Searching
MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 1975 to July 2007. Search terms were reported. Bibliographies of trials, review articles, abstracts, proceedings of meetings, and the manufacturers of heparins (including both low molecular weight heparins and unfractionated heparin) were also searched.

Study selection
Randomised controlled trials (RCTs) that compared subcutaneous low-molecular weight heparins with intravenous unfractionated heparin as adjunctive therapy, in patients with acute ST-segment elevation myocardial infarction (STEMI) who received aspirin and fibrinolytic therapy, were eligible for inclusion. To be eligible the following outcomes had to be reported: death, reinfarction and bleeding in-hospital or at approximately day seven and at day 30. The follow-up period had to be from five days to three months. Trials that compared low molecular weight heparins or unfractionated heparin treated patients with untreated patients or placebo groups were excluded. Low-molecular weight heparins allowed were enoxaparin and dalteparin.

The primary outcome was the composite death from any cause or non fatal recurrent myocardial infarction in the first 30 days after randomisation. The secondary outcome was composite death from any cause, non-fatal myocardial infarction, and major bleeding (definition provided), all during index hospitalisation or at seven days.

The patients in the included trials had STEMI or left bundle branch block, mostly treated after less than six hours. Included patients' age was over 18 years; details of their sex were not provided. Enoxaparin was the low-molecular weight heparin used in all but one of the included RCTs, all of which initially administered an intravenous bolus of 30 to 40mg, with subsequent subcutaneous injections of enoxaparin for up to eight days. For the dalteparin RCT, the initial intravenous bolus was 90 IU/kg, followed by further intravenous injections for up to seven days. Comparative unfractionated heparin regimes were described and were over two to four days. The fibrinolytic therapy included tenecteplase, tissue plasminogen activator or streptokinase; all but one trial also used aspirin at a dose range of 75 to 325mg/day. Follow-up was for 30 days in the majority of the trials (range five to 90 days).

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The authors reported data relevant to trial design, randomisation, blinding and follow-up and compared the demographics and baseline characteristics of the comparative groups.

The authors did not state how many reviewers performed the validity assessment.
Data extraction
The number of events for each outcome was extracted and used to calculate relative risk (RR) and 95% confidence intervals (CI).

The authors did not report how many reviewers performed the extraction.

Methods of synthesis
Relative risks were pooled using a fixed-effects model (Mantel Haenszel). Between trial heterogeneity was determined using the Cochrane Q statistic, when heterogeneity was present (if p>0.05) for each outcome. A second meta-analysis was performed excluding the largest trial.

Results of the review
Seven relevant RCTs were identified (n=27,577 patients, range 242 to 20,506). All the RCTs had adequate allocation concealment; all, but one of the smaller trials (which did not report this data), had a loss to follow-up of less than 1%; one RCT was double blind and the others were all open label RCTs.

Low-molecular weight heparins significantly reduced reinfarction compared with unfractionated heparin during hospitalisation at seven days (RR 0.55, 95% CI 0.47 to 0.63) and at 30 days (RR 0.67, 95% CI 0.60 to 0.76). There were no significant differences for mortality at seven or 30 days with the two interventions.

Unfractionated heparin significantly reduced the risk of major bleeding events at seven days compared with low-molecular weight heparins (RR 1.40, 95% CI 1.18 to 1.67) and minor bleeding events at seven days (RR 1.23, 95% CI 1.13 to 1.34).

After exclusion of the largest trial, the overall results did not change for reinfarction at seven and 30 days, but the meta-analysis for major bleeding at seven days was no longer significant.

Authors’ conclusions
The present meta-analysis suggested that, in patients receiving fibrinolytic therapy for ST-segment elevation myocardial infarction, low-molecular weight heparins were superior to unfractionated heparin as adjunctive therapy in reducing reinfarction during hospitalisation at seven days and at 30 days. Mortality was not significant between the two groups during hospitalisation at seven days and at 30 days. However, unfractionated heparin was superior to low-molecular weight heparins in the reduction of major bleeding at seven days index hospitalisation.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched, and it appeared that unpublished studies were considered. However, it was not clear if any language restrictions were applied, so some studies may have been missed. Publication bias was not assessed. Some relevant data for trial quality were provided. It was not clear whether efforts were made to reduce error and bias in the review process.

Relevant trial details were reported, but with minimal details of the age of the participants and no details of their sex. Statistical heterogeneity was assessed and none was found. The statistical method used for the meta-analysis of the RCTs seemed appropriate and a sensitivity analysis was performed. The results displayed in the figures for the sensitivity analysis did not agree with the text.

In view of limitations arising from the reporting of review process, the extent to which the authors’ conclusions are reliable is unclear.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors identified a need for studies comparing different durations of heparin therapy to identify the
optimal duration.

**Funding**
None.

**Bibliographic details**

**PubMedID**
19609890

**DOI**
10.1002/clc.20432

**Original Paper URL**
http://onlinelibrary.wiley.com/journal/122512860/abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anticoagulants /adverse effects /therapeutic use; Drug Therapy, Combination; Evidence-Based Medicine; Fibrinolytic Agents /adverse effects /therapeutic use; Hemorrhage /chemically induced; Heparin, Low-Molecular-Weight /adverse effects /therapeutic use; Hospitalization; Humans; Length of Stay; Myocardial Infarction /drug therapy /mortality; Platelet Aggregation Inhibitors /therapeutic use; Randomized Controlled Trials as Topic; Recurrence; Risk Assessment; Thrombolytic Therapy /adverse effects /mortality; Time Factors; Treatment Outcome

**AccessionNumber**
12009108310

**Date bibliographic record published**
18/11/2009

**Date abstract record published**
21/04/2010

**Record Status**
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.