Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis

CRD summary
The review concluded that enoxaparin seemed to be superior to unfractionated heparin in reducing mortality and bleeding outcomes during percutaneous coronary intervention, particularly for primary intervention in patients with ST elevation myocardial infarction. The authors' conclusions appear reasonable and are likely to be reliable.

Authors' objectives
To determine the efficacy and safety of enoxaparin compared with unfractionated heparin during percutaneous coronary intervention.

Searching
PubMed and the Cochrane Database of Systematic Reviews were searched from January 1996 to May 2011; search terms were reported. It appeared that there were no language restrictions. Clinical experts were contacted. Abstracts from the following meetings were checked: American Heart Association, American College of Cardiology, European Society of Cardiology, and Transcatheter Cardiovascular Therapeutics.

Study selection
Eligible studies were cohort studies and clinical trials that compared enoxaparin with unfractionated heparin in coronary heart disease patients undergoing primary, secondary (post-fibrinolysis), or scheduled percutaneous coronary intervention according to a predefined protocol. Studies had to report results for mortality and major bleeding.

In the included studies, percutaneous coronary intervention was carried out either following ST elevation myocardial infarction, initial reperfusion with lytics, or in an elective setting. Definitions of myocardial infarction varied. In most studies around a quarter of patients were women and around a fifth had diabetes. Most studies used enoxaparin as an intravenous bolus just before percutaneous coronary intervention at a low dose (0.5mg/kg) or a higher dose (0.75mg/kg or 1mg/kg). The dose range of unfractionated heparin was 60 to 100 IU/kg (bolus) according to the concomitant use of platelet glycoprotein IIb/IIIa inhibitors. Most studies used additional antiplatelet drugs (all but study one used aspirin; clopidogrel and glycoprotein IIb/IIIa inhibitors were also frequently used).

The authors did not state how many reviewers selected studies.

Assessment of study quality
Randomised controlled trials (RCTs) were assessed based on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. A global assessment of risk of bias was graded as being low, unclear, or high. A quality score (out of 9 points) for non-randomised studies and subanalysis and retrospective analysis of RCTs was determined according to the Newcastle-Ottawa scale for cohort studies.

Two reviewers independently evaluated study quality with disagreements resolved through consensus.

Data extraction
Data were extracted to calculate relative risks (RR) with 95% confidence intervals (CI). Investigators were contacted for further data or clarification where necessary.

Two reviewers independently extracted data with disagreements resolved through consensus.

Methods of synthesis
Meta-analyses were performed to calculate pooled relative risks, using a random-effects model. Number needed to treat (NNT) and absolute risk reductions (ARR) were also calculated. Heterogeneity was assessed using the Cochran Q test.

Sensitivity analyses examined the effect of removing each study in turn, and assessed effects in patients with ST
elevation myocardial infarction undergoing percutaneous coronary intervention (primary or secondary), published (full length) studies, small (<500 patients) versus large studies (≥500 patients), intravenous versus subcutaneous enoxaparin, and high quality (RCTs) or low quality studies (registry based).

Publication bias was assessed using a funnel plot and Egger's test.

**Results of the review**
Twenty-three studies were included in the review (the authors reported n=30,966 patients), consisting of 11 RCTs (n=6,735) and 12 non-randomised studies (n=24,284). Many of the non-randomised studies were retrospective analyses or sub-studies of RCTs. Most studies had short follow-up periods (while in hospital or 30 days). Seven RCTs had a low global risk of bias and in four trials the risk was unclear. Most of the non-randomised studies scored 8 or 9 points out of 9 using the Newcastle-Ottawa scale.

Treatment with enoxaparin was associated with statistically significant reductions in death (RR 0.66, 95% confidence interval 0.57 to 0.76; NNT=60; ARR=1.66%; 23 studies), the composite of death or myocardial infarction (RR 0.68, 95% CI 0.57 to 0.81; NNT=50; ARR=2.01%; 21 studies), complications of myocardial infarction (RR 0.75, 95% CI 0.66 to 0.85; NNT=66; ARR=1.52%; 23 studies), and major bleeding (0.80, 0.68 to 0.95; NNT=83; ARR=1.20%; 22 studies). None of these analyses were associated with any significant heterogeneity.

Most of the sensitivity analyses confirmed the main results, although the treatments were not statistically significantly different for mortality in small studies, and for major bleeding in studies giving subcutaneous enoxaparin, RCTs, and small studies. Treatment effects were generally greater in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction.

There was no evidence of publication bias.

**Authors’ conclusions**
Enoxaparin seemed to be superior to unfractionated heparin in reducing mortality and bleeding outcomes during percutaneous coronary intervention, particularly in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant studies in any language were undertaken by searching only two databases (one of them a database of systematic reviews). Although this was supplemented by searching conference abstracts, it was possible that the limited database search may have resulted in relevant studies being missed. No evidence was found of publication bias. Suitable methods were employed to reduce the risks of reviewer error and bias for the processes of data extraction and assessing study quality, although the authors did not report on whether such methods were used to select studies for inclusion.

Study quality was assessed; the results were used for sensitivity analyses. Sufficient study details were provided. Appropriate methods were used to pool data and assess for heterogeneity.

Based on the studies identified, the authors’ conclusions appear reasonable and are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that their results should influence the next guidelines dealing with anticoagulation in percutaneous coronary intervention or in ST elevation myocardial infarction.

**Research:** The authors stated that a head-to-head comparison between intravenous enoxaparin and intravenous bivalirudin was needed in the setting of primary percutaneous coronary intervention (using the techniques of radial access, last generation of stent, and thromboaspiration) and new antiplatelet agents such as prasugrel or ticagrelor.

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