Intravenous low-molecular-weight heparins compared with unfractionated heparin in percutaneous coronary intervention: quantitative review of randomized trials


CRD summary
This review concluded that the use of low molecular weight heparins during percutaneous coronary intervention reduces the risk of major bleeding compared with unfractionated heparin, and is as efficacious. The findings should be treated with some caution, owing to a number of methodological weaknesses in the conduct of the review and clinical variation between the included studies.

Authors' objectives
To compare the efficacy and safety of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) as anticoagulants during percutaneous coronary intervention (PCI).

Searching
MEDLINE was searched from January 1998 to September 2006; the search terms were reported. The reference lists of relevant publications, including reviews, and conference proceedings from major international cardiology meetings were screened, and experts and trial investigators consulted.

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

Specific interventions included in the review
Studies comparing single-bolus intravenous LMWH (initiated at the start of PCI) and intravenous UFH during PCI were eligible for inclusion. No restrictions were applied to the PCI setting, rate and type of stent placement, or use of concomitant antiplatelet therapies. In most of the included studies PCI was performed in either an elective or an urgent setting; in others only elective PCI was performed. Enoxaparin was the LMWH used in the majority of included trials, with dosages ranging from 0.5 to 1 mg/kg.

Participants included in the review
Studies of patients undergoing elective or urgent PCI were eligible for inclusion in the review.

Outcomes assessed in the review
Studies reporting data on efficacy or safety end points were eligible for inclusion. Safety end points included major bleeding, minor bleeding, and a composite measure of major and minor bleeding; the definitions of bleeding used in the studies were reported. Efficacy end points included death, myocardial infarction (MI), urgent target vessel revascularisation, and a composite measure of ischaemic events (death or MI).

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
The authors did not state how validity was assessed, or how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data from the included studies on an intention–to-treat basis. The effect size for each trial was calculated as an odds ratio (OR) with 95% confidence interval (CI).

Methods of synthesis
How were the studies combined?
Pooled ORs with 95% CIs were calculated for each outcome using a random-effects model. A composite of efficacy and safety end point, based on the composite efficacy end point and major bleeding, was calculated. Publication bias was assessed using funnel plots.

**How were differences between studies investigated?**
Statistical heterogeneity was assessed using the Cochran Q test, with a p-value of less than 0.05 indicating statistically significant heterogeneity. Sensitivity analysis was performed by sequentially removing each study from the analysis.

**Results of the review**
Thirteen RCTs (n=7,318) were included.

Major bleeding was significantly less likely with LMWH than with UFH (13 studies; pooled OR 0.57, 95% CI: 0.40, 0.82, p=0.002; no significant heterogeneity, p=0.77). The funnel plot showed no evidence of publication bias. The result was robust to the sensitivity analysis.

There was no statistically significant difference between LMWH and UFH in the risk of minor bleeding (OR 0.75, 95% CI: 0.47, 1.20, p=0.24) or in the composite outcome of major or minor bleeding (OR 0.73, 95% CI: 0.50, 1.05, p=0.09).

There was no statistically significant difference between LMWH and UFH in the composite outcome of death and MI (13 studies; OR 0.99, 95% CI: 0.79, 1.24, p=0.93; no significant heterogeneity, p=0.47). The funnel plot showed no evidence of publication bias.

There was no statistically significant difference between LMWH and UFH in the incidence of death, MI or urgent target vessel revascularisation (OR 1.02, 95% CI: 0.85, 1.22, p=0.87).

The composite efficacy and safety end point showed no statistically significant difference between LMWH and UFH (OR 0.91, 95% CI: 0.78, 1.08, p=0.29).

**Authors’ conclusions**
Use of intravenous LMWH during PCI is associated with a significantly reduced risk of major bleeding without compromising efficacy.

**CRD commentary**
This meta-analysis addressed a well-defined research question using explicit inclusion criteria. Only one (mainly English language) electronic database was searched and this might have led to some relevant studies being missed, although there was no evidence of publication bias in the funnel plots. Steps were taken to limit bias in the study selection and data extraction processes. The validity of the included studies was not assessed, so it is not possible to tell how reliable the findings of the included studies are. The included studies, as the authors noted, were clinically heterogeneous, with trial-defined, rather than standardised outcomes, being pooled. Although there was no evidence of statistical heterogeneity in the meta-analyses, the findings should still be treated with some degree of caution given the clinical heterogeneity, lack of a validity assessment and risk of publication bias.

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

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