Comparison of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing an invasive strategy: a meta-analysis of randomized clinical trials

CRD summary
This review found that anticoagulation with bivalirudin resulted in a reduction in major bleeding episodes but otherwise similar ischaemic events compared to use of unfractionated heparin or enoxaparin with glycoprotein IIb/IIIa inhibitors. Methodological or reporting flaws mean the results and authors’ conclusions may not be reliable.

Authors’ objectives
To assess the safety and efficacy of bivalirudin compared to unfractionated heparin or enoxaparin plus glycoprotein IIb/IIIa inhibitors in patients who underwent percutaneous coronary intervention (PCI).

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from 2000 to 2009 for fully published studies in peer-reviewed journals in English; search terms were reported. Science Citation Index was used to identify further studies.

Study selection
Randomised controlled trials (RCTs) that compared use of bivalirudin with provisional use of glycoprotein IIb/IIIa inhibitors to unfractionated heparin or enoxaparin plus glycoprotein IIb/IIIa inhibitors in patients who underwent PCI were eligible for inclusion. Follow-up needed to be at least 48 hours. The primary outcome was major adverse cardiovascular events defined as a composite of death, myocardial infarction and repeat revascularisation. Secondary endpoints were individual incidences of death, myocardial infarction, repeat revascularisation and major bleeding.

Patients in the selected trials had non-ST elevation acute coronary syndrome, unstable angina, ST-elevated myocardial infarction or underwent elective PCI. Sixty-six to 77% of the trial participants were men, 26% to 45% had a history of prior PCI and 11% to 40% of the patients had a history of prior coronary artery bypass graft (CABG) surgery. One trial excluded patients with acute myocardial infarction. Follow-up ranged from 48 hours to 30 days. Doses of bivalirudin were bolus doses of 0.5 to 0.75mg/kg with infusions of 1.75mg/kg/hour. Heparin doses ranged from 50-70 U/kg bolus. Enoxaparin doses were given in some trials at a dose of 0.5 or 1mg/kg. Administration rates of provisional glycoprotein IIb/IIIa inhibitors ranged from 7.2% to 24%. Study protocols recommended a loading dose of clopidogrel before the PCI procedure except in one trial where administration was left to the discretion of the investigators.

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

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

Data extraction
Three reviewers independently extracted data to calculate odds ratios (OR) and 95% confidence intervals (CI).

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using a fixed-effect model. The reviewers assessed statistical heterogeneity across the studies using Cochran’s Q.

Results of the review
Five RCTs (19,772 patients, range 268 to 13,819) were included in the review.

There were no significant differences observed between the bivalirudin and heparin groups for major cardiovascular events, mortality, myocardial infarction and in rates of urgent revascularisation. Risk of major bleeding was significantly lower with bivalirudin compared to heparin plus glycoprotein IIb/IIIa inhibitors (OR 0.55, 95% CI 0.44 to 0.69).
Some evidence of statistically significant heterogeneity across the studies was reported for mortality (p=0.05).

**Authors' conclusions**
Anticoagulation with bivalirudin resulted in a reduction in major bleeding episodes but otherwise similar ischaemic events compared to use of unfractionated heparin or enoxaparin with glycoprotein IIb/IIIa inhibitors.

**CRD commentary**
The review addressed a clear question. Criteria for inclusion of studies were defined clearly and reproducible. Appropriate databases were searched to identify relevant studies. The restriction of the review to studies published in peer-reviewed journals meant there was a risk of publication bias. Exclusion of studies published in languages other than English meant there was a risk of language biases. The reviewers took steps to minimise errors and bias for data extraction; no such steps were reported for study selection. Methodological quality of the included studies was not evaluated and numbers of events for each outcome were not presented, so it was difficult to assess the reliability of the results.

The reviewers' decision to combine the results in a meta-analysis appeared justified. Although the authors' conclusions were based on the evidence presented, the lack of information about the quality of the included trials and potential for biases mean the authors' conclusions may not be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that pretreatment with thienopyridines in patients given bivalirudin may play an important role in platelet inhibition and provide similar protection from ischaemic events compared with heparin plus glycoprotein IIb/IIIa inhibitors.

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

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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.