Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials


Authors' objectives
To assess the clinical efficacy and safety of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes (ACS) who were not routinely scheduled to undergo early coronary revascularisation.

Searching
MEDLINE was searched from 1990 using the terms 'unstable angina', 'myocardial infarction' and 'platelet aggregation inhibition'. The reference lists of the identified articles were examined, as were the scientific sessions abstracts in Circulation, the Journal of the American College of Cardiology and the European Heart Journal.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs) that had enrolled at least 1,000 participants.

Specific interventions included in the review
Comparisons of glycoprotein IIb/IIIa inhibitors with placebo or control therapy were eligible. The intravenous glycoprotein IIb/IIIa inhibitors used in the included studies were tirofiban (0.4 to 0.6 microg/kg bolus plus 0.1 to 0.15 microg/kg per minute infusion), lamifiban (300 to 500 microg bolus plus 1 to 1.3 microg/minute infusion), eptifibatide (180 microg/kg bolus plus 1.3 microg/kg per minute infusion) and abciximab (250 microg/kg bolus plus 0.123 microg/kg per minute infusion). Concomitant medication included heparin or 'placebo heparin' in some studies. The control groups received either placebo or placebo and heparin. The duration of the infusion ranged from 24 to 120 hours.

Participants included in the review
Participants with acute coronary syndromes, without persistent ST-segment elevation, and who were not routinely scheduled to undergo early coronary revascularisation, were eligible. In the included studies, the mean age of the participants was 64 years, 65% were men, and 76% had a history of cardiovascular disease. In addition, 56% of the participants presented with ST-segment depression, 46% with raised creatine kinase MB concentrations, and 80% with either of these features.

Outcomes assessed in the review
The primary end point for efficacy was a composite of death or nonfatal myocardial infarction (MI). The definition of MI differed between the trials; however, the trial-specific definition was applied for practical reasons. The primary end point for safety was major bleeding. This was not defined but, again, trial-specific definitions were used. The outcomes in the included studies were given at 5 and 30 days. The outcomes described included death, nonfatal MI, death or MI, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) and any event (i.e. death, MI, CABG, PCI).

How were decisions on the relevance of primary studies made?
The authors state that the methodological principles for meta-analysis of IPD from RCTs have been published elsewhere (see Other Publications of Related Interest). Therefore, they only briefly describe the methods used.

Assessment of study quality
The data were checked for completeness, for internal consistency of the patients' records and for consistency with published reports. The baseline characteristics of the participants were checked for any important differences between
the treatment and control groups. The completeness of the data for the main outcomes at 5 days after randomisation was also checked. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

**Data extraction**

An electronic database of IPD from each study was compiled. The categories of data included: baseline characteristics, allocated trial medication, dates and times of randomisation, death, MI, CABG, PCI, stroke, intracranial haemorrhage, major bleeding and 30-day follow-up.

In the paper, the following details of the included studies were tabulated: study identification, enrolment period (years), the number of patients, diagnostic criteria, study medication, additional management, efficacy end points, safety end points, and outcome events at 5 and 30 days. The tables also showed the odds ratios (ORs) of 30-day death or MI in subgroups of patients, according to important clinical baseline characteristics.

**Methods of synthesis**

How were the studies combined?
The pooled ORs were calculated (Cochran Mantel-Haenszel method) and the frequency of events over time was studied (Kaplan-Meier method). Simple Cox's proportional hazard regression models were used to assess the differences between glycoprotein IIb/IIIa inhibitors and placebo or control in the frequency of events over time. The reported hazard ratios and 95% confidence intervals (CIs) were adjusted for between-trial outcome differences. In 'time to event' analysis, events were included until the time of PCI or CABG, if any such procedure was carried out.

Analyses were also conducted in subgroups of participants, according to predetermined adverse cardiac risk factors. The treatment effects were assessed by simple logistic regression models, with adjustments for between-trial outcome differences.

How were differences between studies investigated?
The statistical evidence of heterogeneity between the trial-specific ORs was examined using the Breslow-Day test. Multivariable logistic regression models were applied to estimate adjusted treatment effects in relation to predictive baseline characteristics.

**Results of the review**

Six studies (31,402 participants) were included.

**Efficacy.**

When compared with placebo, at 5 days post-randomisation glycoprotein IIb/IIIa inhibitors were associated with a highly significant 16% relative reduction in the odds of death or MI (OR 0.84, 95% CI: 0.77, 0.93, p=0.0003). This risk reduction was largely maintained until 30 days' follow-up, but with no additional risk reduction (OR 0.91, 95% CI: 0.85, 0.98, p=0.015). There was no statistical evidence of heterogeneity in the treatment effect among separate trials at either time point (p=0.81 and p=0.34). Similar results were seen when the analyses were restricted to trial groups that assessed the efficacy of glycoprotein IIb/IIIa inhibitors additional to heparin, or when tested against heparin. An event reduction was seen in both components of the composite end point (i.e. death and MI). The relative treatment benefit was similar in subgroups of patients (divided by patient baseline clinical characteristics), and thus the absolute treatment benefit was largest in high-risk patients.

**Safety end points.**

At 30 days, compared with placebo or control, major bleeding complications were increased with glycoprotein IIb/IIIa inhibitors (OR 1.62, 95% CI: 1.36, 1.94). Intracranial bleeding was a rare complication in the studies. Glycoprotein IIb/IIIa inhibitors were not associated with a significantly higher rate of intracranial haemorrhage, nor with an increased incidence of total stroke. Full details of all the results were tabulated in the paper.
Authors' conclusions
Glycoprotein IIb/IIIa inhibitors reduced the occurrence of death or MI in patients with acute coronary syndromes not routinely scheduled for early revascularisation. The event rate was greatest in patients at high risk of thrombotic complications.

CRD commentary
The aims of this review were clear. The sources searched were limited, but as the inclusion criteria stipulated trials of at least 1,000 participants, it is unlikely that any studies were missed. The authors did not say why they chose only large trials or how many smaller ones were excluded. Full details of the methods of the review were not given, although the authors provided a reference for the methodology of IPD reviews. Details of the trials and the results were tabulated fully and clearly.

Implications of the review for practice and research
Practice: Treatment with glycoprotein IIb/IIIa inhibitors might be considered, especially in high-risk patients, early after admission and continued until a decision is made about early coronary revascularisation.

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

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The authors state that although the trials were sponsored by several pharmaceutical companies, the review was initiated by the authors and conducted independently of these sponsors, and no separate industrial or non-industrial grant was obtained to conduct the review.

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Other publications of related interest


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