Efficacy and safety of glycoprotein IIb/IIIa inhibitors during elective coronary revascularization: a meta-analysis of randomized trials performed in the era of stents and thienopyridines

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CRD summary
This generally well-conducted review concluded that use of glycoprotein IIb/IIIa inhibitors during elective modern percutaneous coronary intervention seemed safe and effective. Potential for missed studies due to the limited search, selection bias during study selection and methodological limitations of a large proportion of the included trials should be kept in mind when considering the results and conclusions of the review.

Authors' objectives
To investigate the efficacy and safety of glycoprotein IIb/IIIa inhibitors (GPIs) during elective percutaneous coronary intervention (PCI).

Searching
MEDLINE was searched without language restrictions from inception to February 2010; search terms were reported. Reference lists of prior meta-analyses, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched.

Study selection
Randomised controlled trials that compared GPI to placebo or usual care without a GPI in patients who underwent elective PCI were eligible for inclusion. Eligible trials routinely used coronary stents and periprocedural thienopyridines. Trials that directly compared two GPIs or different routes of GPI administration or recruited patients with acute coronary syndrome were excluded. The primary outcomes were non-fatal myocardial infarction, major bleeding and all-cause mortality. Secondary outcomes were urgent revascularisation, stroke, minor bleeding and thrombocytopenia (definitions provided).

Studies were published between 1998 and 2009. Mean age of participants ranged from 54 to 69 years. From 12% to 55% of participants were female. From 8% to 100% of participants had diabetes. From 11% to 72% of participants had prior myocardial infarction. The most commonly used GPI was abciximab 0.25μg/kg bolus followed by 0.125μg/kg/min; tirofiban 10μg/kg bolus followed by 0.15μg/kg/min was also commonly evaluated. Where reported, the delay between PCI and commencement of GPI ranged from eight to 36 hours. Up to 10% of participants in the control arm received GPI. Most studies administered 300mg or 600mg clopidogrel prior to a PCI. Unfractionated heparin was administered using various regimens.

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
Study quality was assessed in terms of adequate description of treatment allocation, blinded outcome assessment and description of losses to follow-up.

It appeared that the quality assessment was conducted during data extraction and, therefore, by two independent reviewers who resolved disagreements by discussion.

Data extraction
Two independent reviewers extracted data to calculate risk ratios (RR) and 95% confidence intervals (CI). Data on all-cause mortality was measured within 30 days and at six to 12 months; all other outcomes were measured within 30 days. Disagreements were resolved by discussion. Study authors were contacted where additional data or clarification were necessary.
Methods of synthesis
Pooled risk ratios and 95% CI were calculated using a DerSimonian-Laird random-effects model. Analyses were conducted for all trials and stratified according to GPI type. Heterogeneity was assessed using Cochran's Q and $I^2$.

Sensitivity analyses were conducted for placebo-controlled RCTs, trials that strictly defined myocardial infarction and trials that use thrombolysis in myocardial infarction major bleeding criteria. Univariate meta-regression was used to explore the effect of thienopyridine use before or after PCI, proportion of diabetics, publication year and dose of heparin. Publication bias was assessed using Begg and Mazumdar's method and Egger's method.

Results of the review
Twenty-two RCTs (10,123 participants, range 46 to 2,159) met the inclusion criteria. Twelve RCTs were placebo-controlled. Fourteen RCTs reported appropriate methods of treatment assignment, 12 reported blinding, but three did not specifically report this was of outcome assessors. Drop-out rates ranged from zero to 8.3% across trial arms.

Overall incidence of non-fatal myocardial infarction was 5.1% with GPI and 8.3% with control (RR 0.66, 95% CI 0.55 to 0.79). Results were similar for abciximab, small molecule GPI and when the analysis was restricted to placebo controlled RCTs.

Incidence of minor bleeding significantly increased with GPI (3.0% versus 1.7%, RR 1.70, 95% CI 1.28 to 2.26; number of RCTs unclear) as did incidence of thrombocytopenia (0.8% versus 0.04%, RR 4.77, 95% CI 1.67 to 13.64; eight RCTs).

There were no significant differences between GPI and control for target vessel revascularisation (10 RCTs), major bleeding (15 RCTs), stroke (five RCTs) and all-cause mortality at either time point (10 RCTs).

There was no significant heterogeneity or evidence of publication bias for any analysis. Results of the meta-regression did not identify any of the variables investigated as effect modifiers.

Authors' conclusions
In the era of elective PCI performed with stents and thienopyridines, GPIs provided clinical benefit. These agents reduced non-fatal myocardial infarction without a notable increase in major bleeding, but increased the risk of minor bleeding. All-cause mortality was not reduced.

CRD commentary
The authors addressed a clear research question supported by appropriate inclusion criteria. Relevant sources were searched without language restrictions. The search was limited and potentially subject to publication bias, but the authors reported that this was not observed. Data extraction was conducted in duplicate; it was unclear whether similar methods for reducing error and bias were employed during study selection. Appropriate criteria were used to assess study quality and the results were reported in full.

The impact of study quality on the results was not reported. Visual inspection of forest plots suggested that there was no obvious relationship between study quality and outcomes. Appropriate methods of synthesis were used; these included relevant subgroup and sensitivity analyses.

This was a generally well-conducted review. But the conclusions should be viewed in the context of the possibility of missed studies due to the limited search, selection bias during study selection and the methodological limitations of a large proportion of the included trials.

Implications of the review for practice and research
Practice: The authors stated that the findings supported guidelines on GPI use and potentially expanded the use of GPIs in appropriate clinical situations.

Research: The authors stated that the potential for GPIs to obviate the need for clopidogrel pre-treatment needed
further study. Newer and more potent agents needed to be investigated as they became available.

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