Meta-analysis of randomized trials of glycoprotein IIb/IIIa inhibitors in high-risk acute coronary syndromes patients undergoing invasive strategy

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CRD summary
The review concluded that, in high-risk acute coronary syndrome patients undergoing an early invasive strategy, upstream glycoprotein IIb/IIIa inhibitors did not improve clinical outcomes and increased the risk of major bleeding compared with selective downstream glycoprotein inhibitors. The authors’ conclusions reflected the evidence base, but lack trial quality reporting and potential bias mean the conclusions should be considered tentative.

Authors' objectives
To compare the upstream to selected downstream administration of glycoprotein IIb/IIIa inhibitors in high-risk patients with acute coronary syndromes undergoing an early invasive strategy.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from January 1990 to March 2010 for relevant studies with no language restrictions; search terms were reported. Google Scholar was also searched. Oral and slide presentations from a number of relevant institution websites were screened from January 2002 to March 2010 to identify further studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared upstream with downstream adjunctive glycoprotein IIb/IIIa inhibitors in high-risk patients with acute coronary syndromes undergoing an early invasive strategy. Primary and secondary endpoints were mortality and myocardial infarction at 30 days; major bleeding complications were assessed as a safety endpoint. Trials were excluded if there was follow-up on less than 90% of participants or if they were ongoing trials or their data were irretrievable.

In included trials, patients received a loading dose of clopidogrel that ranged from 300mg to 600mg. Glycoprotein IIb/IIIa inhibitors included eptifibatide, abciximab and tirofiban. Upstream administration of glycoprotein IIb/IIIa inhibitors ranged from four to 50 hours duration, where reported. Downstream administration of glycoprotein IIb/IIIa inhibitors was mostly left to the discretion of the operator; the mean proportion of patients receiving this treatment ranged from 8 to 100%, where reported.

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

Assessment of study quality
The authors did not state that trials were assessed for quality.

Data extraction
Data were extracted according to the intention-to-treat principle on mortality rate and recurrence of myocardial infarction at 30 days and major bleeding complications; odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Authors were contacted if data were incomplete or unclear.

Two reviewers independently extracted data, with disagreements resolved by consensus.

Methods of synthesis
Trials were pooled in meta-analyses. Summary effect odds ratios with 95% confidence intervals were calculated using the fixed-effect model and the Mantel-Haenszel method. The DerSimonian-Laird random-effects model was to be used where significant heterogeneity was identified. Heterogeneity was assessed using I². Publication bias was assessed by observation of funnel plots.
Results of the review

Seven RCTs (n=19,929 patients) were included in the review. Two of the RCTs had more than 9,000 participants; in the other trials, the number of participants ranged from 160 to 328. Trials were conducted from 2000 to 2008 (where reported).

There was no evidence of differences between upstream and downstream glycoprotein IIb/IIIa inhibitors for mortality rate (mortality OR 1.02, 95% CI 0.84 to 1.24; seven trials) or recurrence of myocardial infarction (OR 0.92, 95% CI 0.82 to 1.02; seven trials) at 30 days. Upstream glycoprotein IIb/IIIa inhibitors were associated with significantly increased major bleeding complications when compared with downstream glycoprotein IIb/IIIa inhibitors (OR 1.44, 95% CI 1.14 to 1.81; seven trials). There was no evidence of heterogeneity in any of the analyses.

There was no evidence of a skewed distribution in the funnel plot, suggesting no publication bias.

Authors' conclusions

In high-risk patients with acute coronary syndrome undergoing an early invasive strategy, treatment with upstream glycoprotein IIb/IIIa inhibitors could not be recommended as it did not improve clinical outcomes and it was associated with an increased risk of major bleeding complications compared with selective downstream glycoprotein IIb/IIIa inhibitor administration.

CRD commentary

The review addressed a clear research question. Inclusion criteria for study design, interventions and outcomes were appropriate; participant criteria were broadly stated, although ‘high-risk’ was not defined. A range of relevant sources were searched to identify applicable studies, with no language restrictions, but no explicit attempts were made to identify grey literature. Although methods used for data extraction were appropriate, the methods used for selection of studies were not described, so reviewer error and bias during study selection could not be excluded.

The quality of the included trials was not assessed, so it was difficult to judge the reliability of the evidence presented. In the included trials, the definition of bleeding complications varied. The proportion of patients receiving downstream administration of glycoprotein IIb/IIIa inhibitors varied between trials and may have reflected differences in the risk profiles of the participants in the trials. Synthesis of the trials in meta-analyses and assessment of heterogeneity and publication bias were appropriate. The authors' conclusion reflected the evidence base, but the interpretation of the results was unclear as some participant details were not reported.

Lack of reporting on the quality of the included trials and potential bias in the review process mean that the authors' conclusions should be considered tentative.

Implications of the review for practice and research

Practice: The authors stated that upstream glycoprotein IIb/IIIa inhibitors cannot be recommended in high risk patients with acute coronary syndromes undergoing an early invasive strategy.

Research: The authors stated further research with long-term follow up was needed.

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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.