Upstream use of small-molecule glycoprotein IIb/IIIa inhibitors in patients with non-ST-segment elevation acute coronary syndromes: a systematic overview of randomized clinical trials


CRD summary
This review concluded that upstream use of intravenous small-molecule glycoprotein IIb/IIIa inhibitors for the treatment of non-ST-segment elevation acute coronary syndromes reduced risk of death or myocardial infarction at 30 days, but there was an increase in major bleeding and transfusion. Overall, despite some limitations identified, the conclusions reflect the evidence presented and appear reliable.

Authors' objectives
To assess the efficacy and safety of intravenous small-molecule glycoprotein IIb/IIIa inhibitors for the treatment of non-ST-segment elevation acute coronary syndromes

Searching
The authors searched PubMed and EMBASE. No dates were given but search terms were provided. References of selected publications were searched to identify additional articles and experts in the field were asked to identify any missing trials.

Study selection
To be eligible for the review, studies needed to be published in English. Randomised controlled trials (RCTs) of upstream small-molecule glycoprotein IIb/IIIa inhibitors for the treatment of non-ST-segment elevation acute coronary syndromes were eligible. Upstream was defined as immediately after random assignment and before cardiac catheterisation. Abciximab was excluded. The comparator was placebo. Trials were excluded if 30 day clinical outcomes were not provided or if they evaluated the use of glycoprotein IIb/IIIa inhibitors only in patients selected to undergo percutaneous coronary intervention. Trials with ST-segment elevation-myocardial infarction patients were not included. The primary efficacy outcome was the composite of death or myocardial infarction at 30 days. Thirty day mortality was also assessed. Primary safety outcomes were major bleeding during hospitalisation and transfusion. The Thrombolysis in Myocardial Infarction (TIMI) bleeding classification was used as the major bleeding endpoint for all trials reporting this outcome. For the remaining trials definitions of major bleeding were trial specific. Included trials were published between 1996 and 2009.

Patients in all trials received aspirin. Agents evaluated were eptifibatide, lamifiban, tirofiban at various regimens.

Assessment of study quality
The authors conducted quality assessment using Delphi criteria.

Data extraction
Data were extracted from publications of the trials and trial databases were accessed for data not shown in the publications. Odds ratios with 95% confidence intervals were calculated for the glycoprotein IIb/IIIa inhibitors versus placebo comparison in each trial.

Methods of synthesis
Odds ratios of all included trials were pooled using meta-analysis with a random-effects model. Trials were then grouped into two categories based on the patient population: trials comparing glycoprotein IIb/IIIa inhibitors versus placebo in patients with non-ST-segment elevation acute coronary syndromes and trials that compared upstream glycoprotein IIb/IIIa inhibitor use versus placebo followed by delayed selective use at the time of percutaneous coronary intervention. These were then pooled separately. Statistical heterogeneity was investigated using the Q statistic and publication bias assessed using a funnel plot.

Results of the review
Twelve RCTs were included in the review (43,674 participants). Eight trials scored 9 out of 9 points on the quality scale, one scored 6 and three scored fewer than 6 points. There was no evidence of publication bias.

**All trials**

Compared to placebo, glycoprotein IIb/IIIa inhibitors reduced the odds of death or myocardial infarction at 30 days (OR 0.89, 95% CI 0.83 to 0.95). Mortality rates were not significantly different between groups (OR 0.93, 95% CI 0.83 to 1.05). Compared to placebo, glycoprotein IIb/IIIa inhibitors increased the risk of major and non-major bleeding (OR 1.23, 95% CI 1.02 to 1.48) and transfusion (OR 1.27, 95% CI 1.17 to 1.38).

**Upstream versus placebo only (seven trials, 24,031 participants)**

Compared to placebo, glycoprotein IIb/IIIa inhibitors reduced the odds of death or myocardial infarction at 30 days (OR 0.88, 95% CI 0.81 to 0.95). Mortality rates were not significantly different between groups (OR 0.89, 95% CI 0.76 to 1.03). Major bleeding increased with the use of glycoprotein IIb/IIIa inhibitors (OR 1.17, 95% CI 0.88 to 1.54) as did transfusion (OR 1.25, 95% CI 1.13 to 1.39).

**Upstream versus delayed use (five trials, 19,643 participants)**

Compared to placebo, glycoprotein IIb/IIIa inhibitors reduced the odds of death or myocardial infarction at 30 days but were not statistically significantly different (OR 0.91, 95% CI 0.82 to 1.01). Mortality rates were not significantly different between groups (OR 1.00, 95% CI 0.81 to 1.23). Major bleeding increased with the use of glycoprotein IIb/IIIa inhibitors (OR 1.34, 95% CI 1.10 to 1.63) as did transfusion (OR 1.31, 95% CI 1.14 to 1.49).

Sensitivity analysis excluding lower quality scores did not alter efficacy findings. Statistically significant heterogeneity was found for major and non major bleeding when all trials were combined.

**Authors’ conclusions**

The upstream use of intravenous small-molecule glycoprotein IIb/IIIa inhibitors for the treatment of non-ST -segment elevation acute coronary syndromes reduced the risk of death or myocardial infarction at 30 days but there was an increase in major bleeding and transfusion.

**CRD commentary**

This review had defined inclusion criteria. Just two databases were searched but the authors used other methods to identify potentially eligible studies. It was unclear if any studies were missed due to the limited electronic search, the restriction to published English language studies and lack of reporting of search dates. Quality was assessed but results were not presented in full. Overall trial quality was good. Study grouping and meta-analyses seemed appropriate. The authors disclosed a number of potential conflicts of interest (listed in the paper).

Despite the limitations identified, conclusions reflect the evidence presented and appear reliable.

**Implications of the review for practice and research**

**Practice**: The authors advised that glycoprotein IIb/IIIa inhibitors should be tailored to patients with most favourable efficacy/risk balance. A selected strategy of periprocedural use of this class of drugs in high-risk patients undergoing percutaneous coronary intervention could optimise the balance of benefit and risk of these agents.

**Research**: The authors recommended using patient-level data to investigate the effects of concomitant use of thienopyridines and percutaneous coronary intervention. Patient-level data could be used to identify subsets of patients with more favourable efficacy versus safety profiles.

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