Upstream vs deferred administration of small-molecule glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: insights from randomized clinical trials

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CRD summary
This generally high-standard review concluded that administration of small-molecule glycoprotein inhibitors prior (upstream) rather than during percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction did not translate into improvements in post-procedural angiographic, clinical or safety outcomes, despite initial epicardial patency improvement. Although there was no discussion of quality issues, these conclusions are likely to be reliable.

Authors' objectives
To evaluate the safety and efficacy of upstream (early) versus deferred small-molecule glycoprotein IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 2000 to August 2009; search terms were provided. Abstract lists from several relevant conferences were searched, as were review articles, editorials and Internet-based sources of information for further relevant studies. All forms of publication were accepted. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared upstream versus deferred administration of small-molecule glycoprotein IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction scheduled for percutaneous coronary intervention were eligible for inclusion. Upstream administration was defined as glycoprotein inhibitor administration as soon as possible following the decision to perform percutaneous coronary intervention (e.g. in the emergency room, ambulance or referral hospital). Deferred administration was defined as glycoprotein inhibitor administration at the time of percutaneous coronary intervention (i.e. in the cardiac catheterisation laboratory). The small-molecule glycoprotein inhibitors tirofiban or eptifibatide were eligible for inclusion.

The primary clinical endpoint was 30-day mortality; incidence of reinfarction and rate of major bleeding complications were also pre-specified clinical and safety endpoints. The primary angiographic endpoint was the combined Thrombolysis in Myocardial Infarction Study (TIMI) grade 2 and 3 flows on the initial angiogram. Pre- and post-procedural TIMI grade 3 flow and TIMI myocardial blush grade 3 were also assessed.

Included trials were evaluated both tirofiban and eptifibatide. Tirofiban was administered as a bolus of 10 or 25µg/kg followed by an infusion of 0.15µg/kg for 24 to 36 hours. Eptifibatide was given as a double bolus of 180mg/kg administered 10 minutes apart followed by an infusion of 2mg/kg⁻¹/min⁻¹ for 12 to 24 hours. All patients were enrolled within six to 24 hours of chest pain onset in the emergency department, referral hospital or ambulance. Included patients had a mean age that ranged from 58 to 68 years; most were male (60 to 85%).

Study selection was performed independently by two authors.

Assessment of study quality
Trias were assessed for adequacy of allocation, use of intention-to-treat analysis and blinded outcome assessment. The criteria recommended by Altman and Schulz and Juni et al were used to assess adequacy of treatment allocation.

Two authors independently performed the data extraction with disagreements resolved by consensus.
Data extraction
The original trial protocol definitions for all outcomes of interest were accepted by the authors; no attempts were made to retrospectively re-categorise outcomes. The intention-to-treat principle was applied.

Two authors independently performed the data extraction with disagreements resolved by consensus.

Methods of synthesis
Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Data were pooled using the Mantel-Haenszel fixed-effect method and the DerSimonian and Laird random-effects method. Heterogeneity was assessed using Cochran's test and $I^2$.

A sensitivity analysis excluding each trial one at a time was conducted for each of the three primary outcomes.

Publication bias was assessed for the primary outcomes (pre-procedural TIMI grade 2 or 3 flow, mortality and major bleeding) using a funnel plot and the adjusted rank correlation test (Begg and Mazumdar).

Results of the review
Ten RCTs including 2,724 patients were included in the review. The results of the validity assessment were not reported.

Clinical and safety endpoints: No statistically significant differences in 30-day mortality, risk of reinfarction or major or minor bleeding were identified between the two modes of small-molecule glycoprotein inhibitor administration. No significant heterogeneity was identified for any of the clinical or safety outcomes.

Angiographic endpoints: Upstream administration of small-molecule glycoprotein inhibitors was associated with statistically significant improvements in pre-procedural angiographic endpoints. An increase in TIMI grade 2 or 3 flow (OR 1.40, 95%CI 1.20 to 1.64), higher pre-procedural TIMI grade 3 flow (OR 2.51, 95%CI 1.61 to 3.92) and improved pre-procedural myocardial perfusion (OR 1.88, 95%CI 1.37 to 2.56) was observed. Substantial heterogeneity was identified for pre-procedural TIMI grade 3 flow ($I^2$=73.9%). No significant effects were seen for post-procedural angiographic or electrocardiographic outcomes and no significant heterogeneity was observed.

The sensitivity analysis showed no effect on overall results when individual trials were omitted from the analysis.

No evidence of publication bias was observed on the funnel plots for the primary outcomes (not presented in the paper) or using the rank correlation test.

Authors' conclusions
Available data did not support routine upstream administration of small-molecule glycoprotein IIb/IIIa inhibitors in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention, as no beneficial effects on post-procedural angiographic or clinical outcomes were identified despite an improvement in initial epicardial patency.

CRD commentary
The aim and inclusion criteria of the review were clearly specified. The literature search was thorough; a reasonable attempt was made to identify unpublished literature. Eligibility of non-English language articles reduced the likelihood of relevant studies being missed. The review methods were well described and appropriate, with all of the main stages of the review conducted in duplicate, which reduced the risk of reviewer bias.

The quality assessment of included trials was described, but results were not presented; the potential implications of any between trial variations in quality were not discussed. Adequate trial details were provided. The approach to trial synthesis was appropriate; heterogeneity and publication bias were thoroughly investigated.

This review was generally conducted to a high standard. The authors’ conclusions were clearly based on the data.
presented and are likely to be reliable, despite the lack of discussion of quality issues.

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

**Practice:** The authors stated that the available data do not support the routine use of upstream small-molecule glycoprotein IIb/IIa inhibitors in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention.

**Research:** The authors stated that further evaluations of small-molecule glycoprotein IIb/IIa inhibitors in trials with larger sample sizes and long-term follow-up are needed to evaluate the long-term clinical outcomes of upstream administration.

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