Routine upstream versus selective downstream administration of glycoprotein IIb/IIIa inhibitors in patients with non-ST-elevation acute coronary syndromes: a meta-analysis of randomized trials


CRD summary
This review found reductions in ischaemic events in patients with non-ST-elevation acute coronary syndromes undergoing invasive cardiac surgery and receiving early (routine upstream) administration of glycoprotein IIb/IIIa inhibitors compared with deferred (selective downstream) administration of glycoprotein IIb/IIIa inhibitors. However, early therapy was associated with increased bleeding complications. The authors' conclusions are likely to be reliable.

Authors' objectives
To compare the outcome of patients with non-ST-elevation acute coronary syndromes receiving routine upstream (at hospital admission and prior to coronary angiography) administration of glycoprotein IIb/IIIa inhibitors versus selective downstream (post-coronary angiography) treatment.

Searching
EMBASE and MEDLINE were searched from January 1990 to May 2009 for relevant studies. Google Scholar and the scientific session abstracts in Circulation, the Journal of the American College of Cardiology, the European Heart Journal and the American Journal of Cardiology were searched for additional studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) of facilitation by upstream administration of glycoprotein IIb/IIIa inhibitors in patients with non-ST-elevation acute coronary syndromes (with at least 100 patients in each treatment arm) were eligible for inclusion. The primary outcome was defined as major adverse cardiac events, which was a composite of death, myocardial infarction and unplanned revascularization at 30 days. The primary safety endpoint was the net adverse cardiac events at 30 days.

In included trials, the proportion of patients with diabetes mellitus ranged from 16% to 30.4%. The percentage of patients undergoing percutaneous coronary intervention ranged from 32% to 59.1%. Upstream treatments consisted of the administration of small molecules, most of which were eptifibatide; tirofiban and abciximab were also used. In downstream treatments, eptifibatide was most commonly used, followed by abciximab and tirofiban. Concomitant antithrombotics taken by the patients included aspirin, bivalirudin, clopidogrel, fondaparinux, low molecular weight heparins and unfractionated heparin. The primary endpoints in the included trials were death, infarction, recurrent ischaemia, and unplanned repeat revascularization.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed using a nine-item checklist that evaluated the adequacy of sequence generation, allocation concealment, blinding, the use of concurrent therapies, treatment of incomplete data, the definition of outcomes, freedom from selective reporting and other biases, and the overall risk of bias.

Data extraction
Data were extracted to calculate odds ratios (OR) and 95% confidence intervals (CI) for the outcomes using intention-to-treat analyses.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using a DerSimonian and Laird random-effects...
model. Statistical heterogeneity was evaluated using the $I^2$ and $X^2$. The Peters test was used to assess the potential for small trial bias and/or publication bias.

Subgroup analyses for the two largest trials were undertaken to assess the results on the basis of gender, presentation with diabetes mellitus and baseline levels of troponin.

**Results of the review**

Five RCTs (19,472 patients) were included in the review. Sample sizes ranged from 220 to 9,406 patients; two trials enrolled 18,613 (96%) of the included patients. In the two largest trials, sequence generation, allocation concealment and the treatment of incomplete data were adequately described. Concomitant therapies were similar between groups and uniform outcome definitions were provided in these trials. The overall risk of bias was regarded as low in one trial and moderate in the other trial. The overall risk of bias was regarded as moderate in the remaining three trials.

**Ischaemic events:** The routine upstream use of glycoprotein IIb/IIIa inhibitors was associated with statistically significant reductions in major adverse cardiac events compared with deferred selective downstream use of glycoprotein IIb/IIIa inhibitors (OR 0.90, 95% CI 0.82 to 0.98; five RCTs; $I^2$=0%), along with significant reductions in recurrent ischaemia and unplanned repeat revascularization (OR 0.78, 95% CI 0.65 to 0.93; three RCTs; $I^2$=0%). There were non-significant reductions in myocardial infarction (five RCTs; $I^2$=0%). There were no differences in mortality between the two strategies (five RCTs; $I^2$=0%).

**Bleeding events:** Significant increases in major bleeding complications were observed with upstream administration of glycoprotein IIb/IIIa inhibitors were observed (OR 1.35, 95% CI 1.11 to 1.63; five RCTs; $I^2$=0%). This was confirmed when major bleeding was classified according to the TIMI scale (OR 1.50, 95% CI 1.18 to 1.90; three RCTs). There were no significant differences observed between the upstream and downstream administration of glycoprotein IIb/IIIa inhibitors for the net adverse cardiac events endpoint (five RCTs; $I^2$=0%).

Subgroup analyses found that patients who showed trends to greater advantages in major adverse cardiac events with upstream administration of glycoprotein IIb/IIIa inhibitors were those who presented with positive troponin or creatine kinase levels (OR 0.89, 95% CI 0.79 to 1.00) and diabetes (OR 0.84, 95% CI 0.70 to 1.01). Significant reductions in major adverse cardiac events were observed for male patients (OR 0.87, 95% CI 0.77 to 0.98), but not in women.

There was no evidence of small-trial bias observed for the major adverse cardiac events outcomes. Some potential for publication bias was observed in the Peters test for the net adverse cardiac events outcomes.

**Authors' conclusions**

The early administration of glycoprotein IIb/IIIa inhibitors in patients with non-ST-elevation acute coronary syndromes was associated with significant reductions in ischaemic events compared with selective deferred administration in patients who underwent invasive cardiac procedures. However, upstream early administration therapy was associated with increases in bleeding complications.

**CRD commentary**

The review addressed a clear question. Some criteria for the inclusion of studies were defined and reproducible. Appropriate databases were searched with no language restriction for relevant studies; there were some attempts to identify studies published as abstracts. The authors did not report steps to minimise errors and biases at any point of the review process.

Methodological quality was assessed and the included trials were judged to be of low to moderate risk of bias. The authors decision to combine the results in a meta-analysis appeared to be justified as there was no statistically significant heterogeneity observed across the trials for the results.

In general, the results and the authors’ conclusions are likely to be reliable despite some reporting limitations.

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

**Practice:** The authors stated that the routine use of upstream glycoprotein IIb/IIIa inhibitors should be reserved for patients at high ischaemic and/or low risk of haemorrhage.
Research: The authors stated that a randomised trial was required that compared upstream and downstream administration procedures in patients who were undergoing coronary angiography and subsequent coronary intervention through the transradial approach, as this approach was associated with reduced access site bleeding.

Funding
Not stated.

Bibliographic details

PubMedID
21035214

DOI
10.1016/j.ijcard.2010.10.010

Original Paper URL
http://www.internationaljournalofcardiology.com/article/S0167-5273(10)00823-5/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Coronary Syndrome /diagnosis /drug therapy; Electrocardiography; Humans; Peptides /therapeutic use; Platelet Aggregation Inhibitors /therapeutic use; Platelet Glycoprotein GPIIb-IIIa Complex /antagonists & inhibitors; Randomized Controlled Trials as Topic; Tyrosine /analogs & derivatives /therapeutic use

AccessionNumber
12012011956

Date bibliographic record published
12/04/2012

Date abstract record published
09/10/2012

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.