Early vs late administration of glycoprotein 11b/111a inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta analysis


CRD summary
This review compared administration at first contact with delayed administration in the catheterisation laboratory. It found a significant benefit of early treatment for angiographic outcomes and trends favouring early treatment for clinical outcomes. The evidence presented supports the authors’ conclusions, but the conclusions should be treated cautiously because the validity of studies included in the review was not assessed.

Authors' objectives
To compare early and late intravenous administration of glycoprotein (Gp) IIb/IIIa in acute ST-segment elevation myocardial infarction (STEMI).

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched for studies published in the last 10 years. Searches for papers presented at major cardiac conferences (details not reported) were also conducted. In addition, experts in the area and drug manufacturers were consulted, and bibliographies were handsearched. No details of any language restrictions were reported.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) in which randomisation occurred outside of the catheterisation laboratory were eligible for inclusion.

Specific interventions included in the review
Studies that compared early administration at the point of initial contact (emergency department or ambulance) and delayed administration (catheterisation laboratory) of Gp IIb/IIIa inhibitors were eligible for inclusion. The agents used in the trials were tirofiban and abciximab. The average time to receiving the drug ranged from 38 to 259 minutes in the early groups, and from 82 to 254 minutes in the late groups.

Participants included in the review
Studies of patients with acute STEMI were eligible for inclusion. The included studies used enrolment criteria of chest pain (less than 6 or less than 12 hours) with ST elevation, or new left bundle-branch block on the electrocardiogram. The mean age of the patients ranged from 59 to 64 years and the proportion of men ranged from 62 to 81%.

Outcomes assessed in the review
The studies had to report outcome data on both culprit artery patency evaluated by Thrombolysis in Myocardial Infarction (TIMI) flow grades on admission and mortality. The primary angiographic end point was the combined TIMI grade 2 and grade 3 flows on the first angiogram, which defined open culprit artery on admission. TIMI grade 3 flow was also assessed separately. The primary clinical outcome was all-cause mortality at the longest follow-up. The composite ischaemic end point at longest follow-up, as defined in the study, was also assessed separately. The clinical outcomes were assessed at between 30 days and 1 year.

How were decisions on the relevance of primary studies made?
Two reviewers independently reviewed abstracts or complete articles.

Assessment of study quality
The authors did not state that they assessed validity.

**Data extraction**
Two reviewers independently extracted the data; the extraction was confirmed by consensus. The results from each trial were those obtained on an intention-to-treat basis.

**Methods of synthesis**
How were the studies combined?
The Mantel-Haenszel fixed-effect method was used to pool odds ratios (ORs). The number of patients needed-to-be-treated (NNT) to avoid one event was calculated for each end point using the overall weighted risk difference.

How were differences between studies investigated?
The Breslow-Day test was used to formally test for heterogeneity.

**Results of the review**
Six studies (n=951: 473 in the early groups and 478 in the late groups) were included.

**Angiographic end points.**
All of the studies reported a greater proportion of patients with TIMI grade 2 or 3 flow in the early groups; this difference was statistically significant for 3 of the 6 trials. The pooled OR was 1.69 (95% confidence interval, CI: 1.28, 2.22, P<0.001), with no statistical evidence of heterogeneity (P=0.23), and the pooled NNT was 8. The proportion of patients with TIMI grade 3 flow was also increased in the early administration group; the pooled NNT was 12.

**Clinical outcomes.**
Four studies reported reduced mortality in the early intervention group compared with the late intervention group, but none of these differences reached statistical significance. The pooled OR was 0.72 (95% CI: 0.37, 1.40, P=0.42), with no statistical evidence of heterogeneity (P=0.34). Similar ORs were reported for the composite ischaemic end point (OR 0.78, 95% CI: 0.51, 1.20, P=0.32) and for MI as an individual component of this end point (OR 0.73, 95% CI: 0.31, 1.77, P=0.64).

The ORs were similar for the two drugs investigated for all outcomes investigated.

The funnel plots suggested that publication or selection bias was unlikely.

**Authors’ conclusions**
In STEMI patients treated with GP IIb/IIIa inhibitors, there appears to have been significant angiographic benefit, with favourable trends for clinical outcomes, when treatment is started at first medical contact before transfer to the catheterisation laboratory. Further evaluations in adequately-powered large trials, to confirm the clinical benefit of this strategy, are awaited.

**CRD commentary**
This was a well-conducted and reported review. It answered a clearly defined question, which was supported by explicit inclusion criteria. Details of the review process were reported and these included attempts to minimise bias. A reasonable literature search was carried out and attempts were made to locate unpublished studies. Further studies may, however, have been located if additional electronic databases had been searched.

Some details of the studies were tabulated. These suggested that the average time to receipt of the drug was actually longer in the early group than in the late group (254 versus 259 minutes) in one of the studies. This was not commented upon in the report, so it is unclear whether this was an error in the paper or a genuine characteristic of this trial. Further
details of the patients in the studies would have helped to assess the generalisability of the results. A limitation of this review was the failure to carry out a quality assessment; it is difficult to draw a firm conclusion from the review without an appreciation of the quality of the included studies. The methods used to pool the results were appropriate and the authors' conclusions are supported by the results presented.

Implications of the review for practice and research
Practice: The authors stated that their data support 'the key role of time to treatment to improve outcomes' and 'the need to develop and/or consolidate prehospital/emergency department systems in the chain of care provided for STEMI patients'.

Research: The authors stated 'further evaluations in adequately-powered large trials are awaited to confirm the clinical benefit of this strategy'.

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