Treatment with tirofiban for acute coronary syndrome (ACS): a systematic review and network analysis

CRD summary
Compared to usual care, tirofiban was more effective for patients with ST elevated myocardial infarction and for patients with non-ST elevated acute coronary syndrome with scheduled percutaneous coronary intervention or medical management. Tirofiban and abciximab were equally effective. Analyses included few studies and a lack of reporting of several study results make the reliability of the conclusions unclear.

Authors' objectives
To compare the efficacy of tirofiban with usual care, eptifibatide or abciximab for patients with acute coronary syndrome.

Searching
Nine databases (including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and DARE) were searched up to March 2010. Several trial registries were consulted. No language restrictions were applied. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that evaluated tirofiban, abciximab or eptifibatide were considered for inclusion. Patients scheduled for percutaneous coronary intervention (PCI) with or without acute coronary syndrome, or patients with ST elevated myocardial infarction (STEMI) or non-ST elevated acute coronary syndrome (NSTE-ACS) treated with GIIb/IIIA as the initial medical management were eligible for inclusion. Studies had to compare intravenous tirofiban, abciximab or eptifibatide as a bolus followed by 12 to 96 hours' infusion with abciximab, eptifibatide or placebo in addition to usual care. Usual care included aspirin and ticlopidine or clopidogrel, and heparin or bivalirudin. Studies that included a mix of diagnoses were excluded where separate data were not reported for each population.

The primary outcome was major adverse cardiac event (such as cardiac death, non-fatal myocardial infarction, revascularisation or other composite endpoint). Additional outcomes included all-cause mortality, number of patients with death or non-fatal myocardial infarction, stroke, myocardial infarction, unstable angina, number of patients who underwent PCI and needed urgent revascularisation, and safety outcomes. Outcomes were prespecified. Follow-up points were in-hospital, 30 days and six months.

Diagnoses varied. Studies focused most often on patients with STEMI, followed by NSTE ACS alone or mixed with STEMI patients, and mixed acute and non-acute coronary syndrome. Treatments were most often administered for patients scheduled for PCI. Tirofiban, abciximab or eptifibatide were administered as a bolus followed by infusion. Dosage varied between studies. Three main bolus doses used for tirofiban were high (25μg/mL), medium (10μg/mL) and low (0.4μg/mL). Infusion doses were classed as high (25μg/kg/min), medium (10μg/kg/min) and low (0.4μg/kg/min).

Two reviewers independently selected references for inclusion. Relevant full texts were screened by one reviewer and checked by a second. Disagreements were resolved by consensus or checked by a second reviewer.

Assessment of study quality
Study quality was assessed using the Cochrane risk of bias tool for randomisation, allocation concealment, blinding, incomplete outcome data and selective reporting.

The quality assessment was carried out independently by two reviewers. Disagreements were resolved through consensus.

Data extraction
Outcomes data were extracted to calculate relative risk (RR) and 95% confidence intervals.

Data were extracted by one reviewer and checked by a second. Disagreements were resolved through consensus.

**Methods of synthesis**

Studies were analysed based on treatment type and doses according to diagnosis. Pairwise comparisons were performed according to tirofiban bolus doses and at a combined dose where possible. Pairwise meta-analysis was performed with a fixed-effect model to pool all available direct comparisons; where this was not possible, indirect comparisons (fixed-effect) and network analysis (Bayesian random-effects) were used. Heterogeneity was assessed with I² and by visual inspection of the forest plots. Studies were not pooled where was heterogeneity was considered high (I²≥76%).

**Results of the review**

Fifty RCTs (more than 52,000 patients, range 60 to 9,461 per trial) were included. Two trials fulfilled all quality criteria but the quality of evidence was generally considered unclear due to limited reporting. Sequence generation was adequate in 16 studies and deemed unclear for 19. Allocation concealment was adequate in 16 studies and not reported for 21 studies. Eleven studies reported adequate patient blinding and seven studies reported adequate physician blinding. Intention-to-treat analysis was used in 31 studies. One study that evaluated eptifibatide for non ST-elevation myocardial infarction-acute coronary syndrome was excluded due to important baseline differences between the study arms.

**Patients with STEMI**: High-dose (25μg/kg/min) and medium dose (10μg/kg/min) tirofiban reduced the risk of major adverse cardiac event at 30 days with patients who underwent planned PCI compared to usual care (high dose RR 0.67, 95% CI 0.45 to 0.99; one trial and medium dose RR 0.28, 95% CI 0.10 to 0.80; one trial). The effect was not statistically significant when given in low dose (one trial) or given as medical management (one trial). At six months, the difference was significantly in favour of medium-bolus tirofiban (RR 0.39, 95% CI 0.19 to 0.78; two trials). There was no evidence of heterogeneity (I²=0%).

**Patients with non ST-elevated acute coronary infarction**: Tirofiban had a positive significant effect on major adverse cardiac event compared to usual care when administered with planned PCI in medium dose (10μg/kg/min) at 30 days (RR 0.39, 95% CI 0.21 to 0.75; three trials) and at six months (RR 0.47, 95% CI 0.27 to 0.79; three trials). Low dose (0.4μg/kg/min) treatments showed a positive in-hospital effect that was not statistically significant (three trials) and no difference at 30 days and six months (two trials). Low doses (0.4μg/kg/min) used as medical management also had significantly more positive results compared to usual care at 30 days (RR 0.58, 95% CI 0.41 to 0.83; three trials) and in hospital (RR 0.48, 95% CI 0.33 to 0.70; three trials). There was no evidence of heterogeneity except for one pairwise comparison (I²=71%).

RCTs and network analysis showed no significant difference in major adverse cardiac event at 30 days and in safety between tirofiban and abciximab. Indirect and network analysis that compared tirofiban with eptifibatide yielded inconclusive results. A risk of thrombocytopenia was reported for low-dose tirofiban in medical management compared to usual care (RR 3.26, 95% CI 1.31 to 8.13). Other secondary outcomes were reported.

**Authors' conclusions**

Compared to usual care, tirofiban was more effective for patients with ST elevated myocardial infarction and for patients with non-ST elevated acute coronary syndrome with scheduled percutaneous coronary intervention or medical management. Tirofiban and abciximab were equally effective and comparisons of tirofiban and eptifibatide were inconclusive.

**CRD commentary**

The review question and study selection criteria were stated clearly. A large number of databases and trial registries were searched. Attempts were made to minimise error and bias during the various stages of the review process.

Study details and results of the quality assessment were reported. Study quality was often unclear due to limited reporting of the studies. One study was excluded due to important baseline differences between the study arms. The extent to which this may have biased the results on eptifibatide was unclear.
The methods of analysis appeared generally appropriate. Results of indirect and network analyses were interpreted with appropriate caution. There was no evidence of heterogeneity but only a very limited number of trials were included in each analysis. Most of the significant study results came from small-size trials of unclear quality from single centres in China which (the authors acknowledged) raised concerns regarding the reliability and applicability of the findings. Several RCTs, including several large trials, were not included in the meta-analyses. It was unclear why their individual results were not reported in a narrative synthesis.

The meta-analyses reported only a limited number of mostly small studies and results from trials excluded from the quantitative analyses were not reported so the reliability of the conclusions is unclear.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: Large multinational trials were needed for better evidence of head-to-head comparisons of tirofiban with other GIIb/IIIa inhibitors and confirm the review findings. Future trials should allow for subanalysis of the influence of pre-treatment with clopidogrel and the types of PCIs. Study design reporting needs considerable improvement. Standardised definitions of major adverse cardiac event as well as upstream and downstream treatment should be developed and implemented.

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