Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials

CRD summary
This review concluded that adjunctive tirofiban reduced clinical outcomes including mortality, but increased minor bleeding, when compared with placebo in patients with acute coronary syndrome or undergoing percutaneous coronary intervention. Compared with abciximab, the effect was less favourable at lower doses, but similar at higher doses. Overall, the review was well conducted and the conclusions appear reasonable.

Authors' objectives
To assess the effects, including regimen and timing of intervention, of tirofiban in people undergoing treatment for coronary artery disease.

Searching
PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched to October 2008. Search terms were reported. Conference proceedings and references of identified studies and reviews were also checked. Citations of identified papers were sought and international experts contacted. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared tirofiban with either placebo or active control, in patients with acute coronary syndrome or undergoing percutaneous coronary intervention, were eligible for inclusion. Trials that failed to report outcomes beyond hospitalisation were excluded.

The primary outcomes of interest were 30-day mortality and long-term mortality rates. Additional outcomes were: myocardial infarction; a composite of mortality or myocardial infarction; major adverse cardiovascular events (death, myocardial infarction or urgent revascularisation); major and minor bleeding (defined according to the Thrombolysis in Myocardial Infarction criteria - TIMI criteria); and thrombocytopenia.

In the included trials participants had ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, non ST-elevation acute coronary syndrome, stable or unstable angina, or were undergoing high risk or elective percutaneous coronary intervention. Tirofiban was given at presentation (upstream) or prior to percutaneous coronary intervention (downstream) as a bolus (10 or 25μg/km or 0.4 or 0.6μg/km per minute) followed by a maintenance dose (01 or 0.15μg/km/minute). Full details of dosages were reported. Active controls were abciximab, bivalirudin or unfractionated heparin. Concomitant treatment in all trials was aspirin and heparin (unfractionated heparin or low molecular weight heparin); in one trial the placebo group received heparin. Some trials also used clopidogrel or ticlopidine.

Three authors independently selected studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
The quality of trials was assessed using the Cochrane Collaboration methods. Generation of randomised sequence, allocation concealment, blinding, concurrent treatment, data completion, definitions, outcome reporting and other potential sources of bias were assessed individually and an overall risk of bias assessment made.

Data extraction
Authors were contacted for missing information where necessary. Odds ratio (OR) and 95% confidence intervals (CI) were calculated.

Three authors independently extracted data. Disagreements were resolved by consensus.
Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using DerSimonian-Laird random-effects model. Numbers-needed-to-treat (NNT) to prevent one event, and numbers-needed-to-harm (NNH) to determine one adverse event, were calculated.

Trials were stratified according to type of control (abciximab versus placebo or usual care), dosage (high versus low) and timing of tirofiban (upstream versus downstream). Subgroup analyses were performed based on type of concomitant therapy (ticlopidine or clopidogrel). Trials that had more than one dosage or timing versus control/placebo were allocated to the most suitable category.

Heterogeneity was assessed using $\chi^2$ and the $I^2$ statistic. Meta-regression was used to investigate possible effects of type of control, drug administration regimen, concomitant therapy, adequate randomisation, concealment of allocation, and blinding of participants to treatment.

Publication bias was assessed by visual inspection of funnel plots and Peters test.

Results of the review
Thirty one RCTs were included in the review with 20,006 participants (12,874 placebo group; 7,132 abciximab group). In the placebo group, seven trials had fewer than 100 participants and four trials had between 1,224 and 3,232 participants. The abciximab group was dominated by one trial of 5,308 participants. Follow-up ranged from hospital stay to 36 months. Assessment of trial quality showed that 12 were at low risk of bias; all others were at moderate risk. Tests showed no evidence of publication bias.

Tirofiban versus placebo or usual care:
At 30 days, tirofiban resulted in a reduction in mortality (OR 0.68, 95% CI 0.54 to 0.86), mortality or myocardial infarction (OR 0.69, 95% CI 0.58 to 0.81), myocardial infarction alone (OR 0.71, 95% CI 0.56 to 0.90) and major adverse cardiovascular events (OR 0.73, 95% CI 0.60 to 0.89) compared with placebo or usual care. The number-needed-to-treat to prevent one death or myocardial infarction at 30 days was 40; the number-needed-to-treat for death was 100. There was moderate heterogeneity for the outcome major adverse cardiovascular events ($I^2=35\%$) but none evident for other outcomes. Tirofiban use increased minor bleeding (OR 1.42, 95% CI 1.13 to 1.79) and thrombocytopenia (OR 1.51, 95% CI 1.06 to 2.16), but there was no significant difference in major bleeding (OR 1.21, 95% CI 0.88 to 1.67). The number-needed-to-harm for major bleeding was 286 for one major haemorrhagic event.

At longest available follow-up (average five months), there was a reduction in mortality (OR 0.81, 95% CI 0.66 to 0.99) and death or myocardial infarction (OR 0.73, 95% CI 0.62 to 0.85).

In subgroup analyses, participants treated with additional clopidogrel or ticlopidine had similar results for 30 day mortality and mortality or myocardial infarction to main analyses.

Tirofiban versus abciximab:
All trials gave tirofiban downstream. There was no evidence of heterogeneity. There was no difference in mortality at 30 days and, although there was some apparent increase in the composite of death and myocardial infarction (OR 1.18, 95% CI 0.96 to 1.45), and major adverse cardiovascular events (OR 1.18, 95% CI 0.97 to 1.44), neither were statistically significant. There was no difference in major bleeding, but there were reductions in minor bleeding (OR 0.64, 95% CI 0.50 to 0.82) and thrombocytopenia (OR 0.28, 95% CI 0.08 to 0.94).

In the subgroup of trials that assessed a higher bolus dose of tirofiban (25μg/km), there was no difference in mortality, death or myocardial infarction, or major adverse cardiovascular events. At the longest available follow-up (all trials), there was no difference in mortality, death or myocardial infarction, or major adverse cardiovascular events.

When tirofiban was compared with abciximab, meta-regression showed a trend for an interaction for the outcome of 30-day death or myocardial infarction, and the bolus regimen of tirofiban suggested more efficacy at the higher dose...
(25μg/km) but this was not statistically significant. No other interactions were identified for the outcomes of 30-day death or myocardial infarction, or long-term major adverse cardiovascular events.

Authors’ conclusions
When compared with placebo, adjunctive tirofiban reduced mortality, the composite outcome of death or myocardial infarction, and major adverse cardiovascular events in patients with acute coronary syndrome or undergoing percutaneous coronary intervention; it also increased minor bleeding and thrombocytopenia. Compared with abciximab, tirofiban was less favourable at lower doses (10μg/km bolus), but had a similar effect at higher doses (25μg/km bolus).

CRD commentary
The aims of the review were clearly stated in terms of participants, study design, treatment and outcomes. However, studies that did not appear to entirely meet the inclusion criteria (in terms of length of follow-up) were included. The search covered a number of relevant sources, including foreign language and unpublished studies, reducing the risk of language or publication bias. The methods of study selection and data extraction were aimed at reducing reviewer error or bias.

Although the authors did not state how many reviewers assessed study quality, an appropriate tool was used. Little information was given about the included participants, so it was not possible to comment on the generalisability of results. The methods of analyses appeared appropriate, although there was no mention of the use of intention-to-treat analyses. Possible heterogeneity was investigated. There were some anomalies in the reporting of trial details, including the possible misclassification of one large trial as placebo controlled.

Overall, the review seems to have been well conducted and the conclusions appear reasonable.

Some of the authors disclosed they had been consultants for various pharmaceutical companies, including Iroko Pharmaceuticals, LLC (the manufacturers of tirofiban).

Implications of the review for practice and research
Practice: The authors stated that findings suggest that tirofiban is an effective option to reduce ischaemic events in people with acute coronary syndromes or undergoing percutaneous coronary intervention.

Research: The authors stated that further research is needed to confirm the effects of tirofiban in people with acute coronary syndromes or undergoing percutaneous coronary intervention. This should include an assessment of the effects of a higher dose bolus just prior to percutaneous coronary intervention.

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