Tirofiban use with clopidogrel and aspirin decreases adverse cardiovascular events after percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized trials

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CRD summary
Routine early tirofiban use plus aspirin and clopidogrel in patients with acute ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention may have reduced major adverse cardiovascular events without increasing major bleeding rates. The conclusions were not definitive due to limited evidence. The authors' conclusions were appropriately cautious and are likely to be reliable.

Authors' objectives
To assess the clinical and angiographic benefits and bleeding risk associated with routine early use of tirofiban for patients treated with dual antiplatelet therapy undergoing primary percutaneous coronary intervention in ST-elevation myocardial infarction.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to February 2010 for published articles in English. References of included studies were consulted for additional studies. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that used aspirin and clopidogrel in addition to tirofiban or control were eligible for inclusion. Patients who underwent primary percutaneous coronary intervention for acute ST-elevation myocardial infarction were included. Studies with less than 90% of patients at follow-up, or with failed or rescue percutaneous coronary intervention were excluded. For studies where more than one dose of tirofiban was used in the intervention arm, the cohorts with the higher dose were included.

Doses and timing of tirofiban and clopidogrel varied. Most of the trials used tirofiban doses of either 10mcg/kg bolus or over three minutes then 0.15mcg/kg/min for between 18 and 36 hours, or 25mcg/kg bolus then 0.15mcg/kg/min for 12 or 18 hours. Clopidogrel was administered orally in doses that ranged from 300 to 600mg before or after stent placement. All participants received aspirin (300 or 500mg) and heparin (various doses). Clinical outcomes included major adverse cardiovascular events, death, reinfarction, revascularization, thrombolysis in myocardial infarction-defined major bleeding, and any bleeding. Angiographic outcomes and adverse events were also reported.

Where reported, major adverse cardiovascular events definitions varied between the studies, but all included death and a measure of infarction and revascularisation.

Two researchers independently selected the studies for inclusion. No significant disagreements were encountered.

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

Data extraction
Data on clinical outcomes and angiographic outcomes were extracted. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for dichotomous data, and mean differences (MDs) and 95% confidence intervals were calculated for continuous data.

Two researchers independently extracted the data. No significant disagreements were encountered.

Methods of synthesis
A fixed-effect meta-analysis was used to pool data; if significant heterogeneity was found, a random-effects model was
adopted. Heterogeneity was assessed using $I^2$, $X^2$ and through visual inspection of confidence intervals. Subgroup analyses were undertaken to account for follow-up duration.

**Results of the review**
Six RCTs were included in the review (1,429 patients). Of those, four trials reported clinical outcomes after percutaneous coronary intervention. Longest reported length of follow-up for clinical outcomes was 30 days for two studies and six months for the other two trials.

The odds of a major adverse cardiovascular event were significantly lower for patients who received tirofiban compared to control (OR 0.5, 95% CI 0.26 to 0.94; four trials). There was evidence of some heterogeneity ($I^2=39\%$).

An analysis of three studies that reported major adverse cardiovascular events at 30 days reported a difference favouring tirofiban that was not statistically significant.

There was a difference in mortality favouring tirofiban that was not statistically significant using a random-effects analysis, but was significant using a fixed-effect analysis (OR 0.43; 95% CI 0.22 to 0.81). Both analyses included three trials and showed evidence of some heterogeneity ($I^2=32\%$).

There was no significant difference in major bleeding between the groups, but a non significant trend toward increased bleeding (any bleeding) with tirofiban was found.

Corrected thrombolysis in myocardial infarction frame count was significantly reduced with tirofiban (mean difference -8.48; 95% CI -12.62 to -4.34; four trials; $I^2=80\%$). The odds of reinfarction and revascularisation were not significantly different between the two groups. Other angiographic outcomes were reported in the review.

**Authors’ conclusions**
Routine early use of tirofiban in addition to dual antiplatelet therapy with aspirin and clopidrogel in patients with acute ST-elevation myocardial infarction who received primary percutaneous coronary intervention may have reduced major adverse cardiovascular events without increasing major bleeding rates. These conclusions were not definitive due to limited evidence.

**CRD commentary**
The review question and inclusion criteria were clear. Several bibliographic databases were searched. Studies that were not published in English were excluded so some studies may have been missed (one non-English study was excluded). It was unclear whether this significantly affected the review findings. Steps were taken to minimise error and bias during study selection and data extraction.

The quality of the evidence was unclear, as the authors did not report that they assessed the validity of the included studies. The number and size of the studies were relatively small, as acknowledged by the authors. However, only studies with randomised allocation and high follow-up rates were included in the review, which limited the risk of selection and attrition biases. Study details were adequately reported. The methods of analysis were appropriate overall, and suitable methods were used to assess heterogeneity.

The conclusions reflected the evidence. The authors appropriately noted that their conclusions were not definitive due to the small size and number of trials. Despite the lack of quality assessment, the review conclusions were likely to be reliable.

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

**Practice:** The authors did not state any implications for practice. They stated that no conclusions could be made regarding optimum dose and duration of tirofiban.

**Research:** The authors stated that a large and adequately powered randomised trial was needed to confirm the review findings, especially in a high-risk ST-elevation myocardial infarction population.

**Funding**
Not stated.
Bibliographic details

PubMedID
21871775

DOI
10.1016/j.cjca.2011.03.017

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Angioplasty, Balloon, Coronary; Aspirin /administration & dosage; Drug Therapy, Combination; Female; Humans; Male; Myocardial Infarction /therapy; Platelet Aggregation Inhibitors /administration & dosage; Randomized Controlled Trials as Topic; Ticlopidine /administration & dosage /analogs & derivatives; Treatment Outcome; Tyrosine /administration & dosage /analogs & derivatives

AccessionNumber
12011007492

Date bibliographic record published
18/04/2012

Date abstract record published
16/08/2012

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.