Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials

Keeley E C, Boura J A, Grines C L

CRD summary
This review assessed primary percutaneous transluminal coronary angioplasty (PTCA) versus intravenous thrombolytic therapy for acute myocardial infarction (AMI). The review found that primary PTCA is more effective than thrombolytic therapy for the treatment of AMI. Limited details on the review process makes it difficult to assess the quality of included studies and verify the reliability of the review conclusion.

Authors' objectives
The primary aim was to ascertain which reperfusion therapy, intravenous thrombolytic therapy or primary percutaneous transluminal coronary angioplasty (PTCA), is most effective for the treatment of patients with acute ST-segment elevation myocardial infarction (AMI). The secondary aims were to assess the effect on clinical outcomes of the thrombolytic regimen used (streptokinase or fibrin-specific therapy), and the strategy of emergent hospital transfer for primary PTCA compared with on-site thrombolysis.

Searching
MEDLINE and scientific session abstracts published in relevant cardiology journals (New England Journal of Medicine, Journal of the American College of Cardiology, Circulation, European Heart Journal, Heart and Clinical Cardiology) were searched for published and unpublished trials. There was no information about the terms used to search MEDLINE.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were available.

Specific interventions included in the review
The inclusion criteria specified comparisons of primary PTCA with thrombolytic therapy. The thrombolytic therapies used in the included studies were streptokinase (1.2 to 1.5 million units) and fibrin-specific treatments such as duteplase, tissue-type plasminogen activator (t-PA) and accelerated t-PA. Accelerated t-PA consisted of 15 mg intravenous bolus followed by an infusion of 0.75 mg/kg body weight over 30 minutes (maximum 50 mg), then 0.50 mg/kg body weight over 60 minutes (maximum 35 mg) for a maximum dose of 100 mg. In addition, stents and platelet glycoprotein Ib/IIa inhibitors were used in 12 and 8 studies, respectively.

Participants included in the review
The inclusion criteria specified people with AMI. The definitions of AMI varied in the included studies, but typically they required ischaemic symptoms and ST segment elevation of at least 1 mm in two contiguous leads or a left bundle branch block. The criteria for time to treatment in the included studies was generally up to 12 hours, but in one study was up to 36 hours. Participants with cardiogenic shock were included in one trial. The ages of the participants in the included studies (where given) were up to 80 years, and in one study the participants were 76 years or older.

Outcomes assessed in the review
The outcomes assessed included total mortality, reinfarction, recurrent ischaemia, total stroke, haemorrhagic stroke, major bleed, as well as the combined end point of death, reinfarction or disabling stroke. Major bleed was defined as intracranial haemorrhage or bleeding that caused haemodynamic compromise or blood transfusion, or both. Outcomes as defined in the original trials were used. Since the same time points were not used in all trials, the end points were defined as short-term (4 to 6 weeks) and long term (6 to 18 months) when available.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

**Assessment of study quality**
The authors state that the principal investigators were contacted to 'ensure validity of the data, obtain additional unpublished data, and verify that the study was randomised'.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted on the patient characteristics, symptom duration, numbers randomised, treatments and outcomes. Details of the treatments included the use of stents and glycoprotein Ilb/IIIa antagonists, the thrombolytic agent used, dosage and administration time, time to treatment, availability of crossover data and numbers crossed over. The outcomes were presented as numbers and percentages for death, nonfatal reinfarction, total stroke, haemorrhagic stroke and the total for death, reinfarction and stroke. All comparisons were based on an intention-to-treat analysis. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each outcome for each study.

**Methods of synthesis**

**How were the studies combined?**
The study results were combined by totalling the actual counts of events in each trial. The combined ORs and 95% CIs were calculated.

**How were differences between studies investigated?**
Where appropriate, chi-squared tests or Fisher's exact tests were performed. One study enrolled patients with cardiogenic shock, so some of the data were also analysed with and without this study. The ORs for each outcome for each study were examined for heterogeneity using the Mantel-Haenszel method; a p-value of 0.05 was considered significant.

**Results of the review**
Twenty-three studies (7,739 participants) were included. Streptokinase was used in 8 studies (1,837 participants) and t-PA in 15 (5,902 participants). The studies included single-centre, multicentre and multinational studies.

Overall, the patients assigned to PTCA were less likely to die (OR 0.73, 95% CI: 0.62, 0.86), have a nonfatal infarction (OR 0.35, 95% CI: 0.27, 0.45), have a haemorrhagic stroke (OR 0.05, 95% CI: 0.006, 0.35) or experience the combined end point of death, reinfarction or stroke (OR 0.53, 95% CI: 0.45, 0.63), than those assigned to thrombolysis. This was true for both short- and long-term outcomes. A subgroup analysis excluding the one trial of patients with cardiogenic shock showed a very similar result for death (OR 0.70, 95% CI: 0.58, 0.85). Major bleed was the only end point for which individuals were at greater risk when treated with primary PTCA (OR 1.30, 95% CI: 1.02, 1.65). When the different thrombolytic therapies used were taken into account, the results indicated that PTCA had better clinical outcomes than either of the drug treatments (full details given in the paper). In the tests for heterogeneity, the p-values were 0.56 for death 0.35 for reinfarction, 0.85 for total stroke, 0.75 for haemorrhagic stroke, and 0.03 for the combined end points (death reinfarction, stroke). A p-value for combined death and reinfarction showed significant heterogeneity, so this end point was excluded.

The combined data for the five studies that compared emergent hospital transfer for PTCA to on-site thrombolysis indicated that PTCA was associated with significant reductions in nonfatal reinfarction, total stroke and the combined end point, and was non significantly associated with decreased death.

**Authors' conclusions**
Primary PTCA is more effective than thrombolytic therapy for the treatment of ST-segment elevation AMI.

**CRD commentary**
This was a clearly written paper with well-defined aims. The database searches were limited to MEDLINE only, and the terms used and dates searched were not given. It is possible that some studies were missed. Details of the review process were not provided, e.g. how the studies were selected, validity judged and data extracted. Thus, it is difficult to judge how valid the included studies were and it is possible that bias may have been introduced. The statistical methods were unusual in that the authors used a combined outcome of actual counts of events from the studies rather than a meta-analysis of the results of individual studies, thus jeopardising the randomisation in the original studies. Also, the decision to exclude a pre-specified outcome of interest because heterogeneity was present, without investigating the causes of that heterogeneity, is somewhat unusual.

The authors' conclusions seem to follow from the evidence presented. No specific funding was available for this review, but the authors state that one of them received unrestricted research grants from Boston Scientific, Guidant and Scimed companies, and has served as a consultant for Aventis and Guidant.

**Implications of the review for practice and research**
The authors did not state any implications for further research and practice.

**Bibliographic details**

**PubMedID**
12517460

**DOI**
10.1016/S0140-6736(03)12113-7

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Angioplasty, Balloon, Coronary; Humans; Myocardial Infarction /drug therapy /mortality /therapy; Randomized Controlled Trials as Topic; Streptokinase /therapeutic use; Thrombolytic Therapy; Treatment Outcome

**AccessionNumber**
12003008039

**Date bibliographic record published**
31/05/2003

**Date abstract record published**
31/05/2003

**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.