Primary coronary angioplasty compared with intravenous thrombolytic therapy for acute myocardial infarction: six-month follow up and analysis of individual patient data from randomized trials

PCAT Collaborators

CRD summary
This review of individual patient data compared primary coronary angioplasty (PTCA) with thrombolysis for acute myocardial infarction. Primary PTCA was more effective than thrombolytic therapy in reducing death, reinfarction, and stroke, with greatest absolute benefits for high risk patients. The conclusions are reliable, but treatment effects varied across the trials raising issues about how widely the results can be applied.

Authors' objectives
To compare the effectiveness of primary percutaneous transluminal coronary angioplasty (PTCA) and thrombolysis in acute myocardial infarction (MI) during a 6-month follow-up period.

Searching
Trials were identified through a computerised bibliographic search of MEDLINE from January 1985 to January 1998. Abstracts of scientific sessions in Circulation, the Journal of the American College of Cardiology, and the European Heart Journal were searched from January 1993 to January 1998. Experts in the field were contacted for any additional published or unpublished studies.

A steering committee and a writing committee (PCAT collaborators) was established to identify trials and undertake the meta-analysis.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs).

Specific interventions included in the review
Comparisons of primary PTCA with intravenous thrombolytic drug therapy. The specific thrombolytic drug therapies were streptokinase, 3- and 4-hour tissue type plasminogen activator (tPA), 90-minute accelerated tPA and duteplase.

Participants included in the review
People with suspected acute MI with an ST elevation of at least 1 mm in two contiguous leads or a left bundle branch block, no major contraindications to the use of thrombolytic drug therapy, and who had been randomised within 6 hours of suspected acute coronary occlusion, were eligible. Male and female participants were included; the median ages were 61 and 62 years, respectively. The co-morbidities recorded were diabetes, previous MI and prior PTCA or coronary artery bypass graft (CABG).

Outcomes assessed in the review
The outcomes assessed were the rates of total mortality, reinfarction, death or nonfatal reinfarction, total stroke, haemorrhagic stroke, major bleeding (requiring transfusion) and CABG.

How were decisions on the relevance of primary studies made?
The relevance of the primary studies was established through communication with trial investigators.

Assessment of study quality
The authors reviewed each trial to assess the validity of randomisation of treatment allocation, exclusions from
analysis, completeness of follow-up data and concealment of outcome assessment. Authors sought clarification for differences between the analysis of the data provided and previously published results. The authors do not state explicitly how judgements of validity were made, in terms of who made the decisions or the criteria used.

Data extraction
The trial investigators provided IPD for their trial. The data requested included: the participants' baseline characteristics; inclusion criteria of the trial; number of participants (in total and in each treatment arm); thrombolytic agent used in the comparator arm; duration of symptoms; duration from symptom onset to PTCA or thrombolysis; duration from symptom onset to randomisation; reoccurrence of MI; total number of strokes; number of haemorrhagic strokes; duration from randomisation to fatal event; duration from randomisation to death or MI; number of participants who died over a follow-up period of up to 30 days; and the number who died over a follow-up period of 6 months.

The 6-month follow-up data missing for two studies were imputed on the basis of the combined event rates between 1 and 6 months' follow-up from the other nine studies. Additional imputed events were distributed into the treatment arms using the treatment effect observed in the shorter follow-up period of the two studies with missing data.

Methods of synthesis
How were the studies combined?
For each outcome, a pooled relative risk (RR) with 95% confidence interval (CI) was calculated by intention-to-treat. Time to event data were analysed using regression methods. Regression methods were also used to categorise the participants as high, intermediate or low risk for subgroup analyses.

A sensitivity analysis was used to assess the effects of missing follow-up data.

Possible effects of publication bias were assessed by calculating the number of additional unpublished trials showing no benefit that would be needed to render the findings of the meta-analysis statistically non significant.

How were differences between studies investigated?
Differences in treatment effect between the studies were investigated by grouping studies in the meta-analyses according to the thrombolytic comparator used, the time from the start of thrombolytic therapy to the first balloon inflation, and the volume of PTCA procedures carried out at the study site annually.

Results of the review
IPD from 10 RCTs (n=2,725) were included; summary data from an additional study (n=90) for which IPD were not available were included in the analysis.

Mortality at 30 days was 4.3% for 1,348 participants randomised to PTCA and 6.9% for 1,377 participants assigned to thrombolytic therapy; there was a statistically-significant difference in favour of PTCA (RR 0.62, 95% CI: 0.44, 0.86, p=0.004). At 6 months the difference was still statistically significant, although imputing missing 6-month follow-up data for two studies in the analysis gave an overall difference that was not statistically significant (RR 0.73, 95% CI: 0.55, 0.98, p=0.04). The combined death and reinfarction rates at 30 days were 7.0% for PTCA and 12.9% for thrombolysis, with a sustained effect at 6 months (RR 0.60, 95% CI: 0.48, 0.75, p<0.0001). The risk of haemorrhagic stroke at 30 days was lower in the PTCA group (RR 0.06, 95% CI: 0.01, 0.5, p=0.009).

The median time to treatment was 47 minutes longer for patients treated with PTCA than for those treated with thrombolytic therapy (p<0.0001).

The rate of major in-hospital bleeding was similar in both treatment groups. The overall 30-day CABG rate was lower in the PTCA group (RR 0.74, 95% CI: 0.56, 0.98, p=0.04). There were insufficient data for analysis at the 6-month follow up.

The relative risk of death or nonfatal MI in the subgroups analysed was similar to the reduction overall. However, the
absolute benefit varied depending upon the baseline risk. The relative treatment effect varied with trial, type of thrombolytic agent, time to PTCA and the recruitment rate of participants.

The authors calculated that to render the 6-month mortality findings non significant would require two additional studies (with about 200 participants each) showing no benefit. To render the 6-month reinfarction findings non significant would require 66 more studies showing no benefit; 68 additional studies would be needed to change the findings for death or nonfatal reinfarction at 6 months.

Authors' conclusions
The authors concluded that primary PTCA has a significant advantage over thrombolysis in reducing mortality at 30 days, with an effect probably maintained to 6 months. There is compelling evidence for a sustained reduction in reinfarction and a major reduction in the risk of haemorrhagic stroke with PTCA. The relative benefits of PTCA over thrombolysis do not appear to vary across a broad cross-section of patients, but the absolute benefits vary markedly according to the baseline risk. Therefore, the extent to which the results can be generalised is unknown.

CRD commentary
The review addressed a clear question in terms of the participants, intervention, outcomes and study design. The strategy undertaken to identify the trials was extensive, and a collaborative group of trial investigators was established to maximise the retrieval of IPD and to conduct the meta-analysis. Summary data for one trial were included in the analysis because IPD were unavailable. This did not appear to influence the findings significantly. The effects of imputing missing 6-month follow-up data was investigated, showing that the 6-month mortality result is uncertain.

The validity of the eligible trials was assessed by checking the raw data from each trial and resolving any problems with the trial investigators. No trials were reported to have failed the data checking procedures. The data appear to have been analysed using appropriate techniques for the meta-analysis of IPD, and the rationale for the subgroup analysis was clear. Heterogeneity was investigated and discussed in the text. The conclusions are supported by the evidence presented, although it appears that data on haemorrhagic stroke were sparse.

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

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