Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis

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Authors' objectives
To compare in-hospital mortality for prehospital versus in-hospital thrombolysis for acute myocardial infarction (AMI).

Searching
Searches were conducted of MEDLINE, EMBASE, and Science Citation Index (1982 to 1999); Dissertation Abstracts (1987 to 1999); and Current Contents (1994 to 1999). Key terms were: 'thrombolysis'; 'thrombolytic therapy'; 'prehospital'; 'acute myocardial infarction'; combined with the Cochrane search strategy (see Other Publications of Related Interest no.1). Bibliographies of texts and journal articles were handsearched and the National Institutes of Health website was reviewed for grants pertaining to the subject. Primary authors and manufacturers of thrombolytic agents were contacted for knowledge of unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible. Reasons for exclusion of identified studies were listed and included duplicate data, lack of randomisation, mortality only reported at 60 days and 2 years, and only cardiac mortality reported.

Specific interventions included in the review
Comparisons of prehospital versus in-hospital thrombolysis were eligible. Thrombotic agents included urokinase, anistreplase, and recombinant tissue-type plasminogen activator. Providers of thrombolysis included intensivists in a mobile intensive care unit, general practitioners (GP) in a rural area, and paramedics.

Participants included in the review
Patients with acute myocardial infarction (AMI) were eligible. Inclusion criteria were similar across studies (chest pain with onset less than 4 to 6 hours ago and lasting at least 30 minutes and not relieved by nitrates, ST-segment elevation or QRS peak or isolated ST level depression or tall T-waves with coronary artery disease) except one study that used the judgment of the GP without interpretation of the electrocardiogram (ECG). Study exclusion criteria included contraindications to thrombolysis and severe hypertension.

Outcomes assessed in the review
The primary outcome was all-cause hospital mortality. Intended secondary outcomes were scene times, time to thrombolytic treatment, postinfarction ejection fraction, Q-wave infarction, and adverse events.

How were decisions on the relevance of primary studies made?
Two reviewers blinded to author's name, journal, and results assessed the relevance using a hierarchical approach based on title, abstract, and the full manuscript. When disagreements arose, the study was included in the next screening level. Inter-reviewer agreement and 95% confidence intervals (CI) were evaluated for each stage of the screening process using a Kappa statistic. Weighted K statistic (SE) was 0.65 (0.09) for titles, 0.87 (0.11) for abstracts, and 0.86 (0.25) for articles.

Assessment of study quality
The Detsky scale was used to assess and score validity (see Other Publications of Related Interest no.2). Two reviewers blinded to author's name, title, introduction, discussion and journal, independently assessed validity. Inter-rater agreement was evaluated using the interclass correlation coefficient for random raters. Interclass correlation coefficient for random raters was 0.73.
Data extraction
Two reviewers blinded to author’s name, title, and journal, extracted the following data: author; year of publication; provider; time from onset to thrombolysis; outcome; and inclusion and exclusion criteria. Abstracted data was confirmed by reviewer consensus and then sent to the primary author for verification if necessary.

Methods of synthesis
How were the studies combined?
A random-effects model was used to estimate a pooled odds ratio (OR) with 95% CIs and number needed to treat (NNT).

How were differences between studies investigated?
Homogeneity was measured using 5 degrees of freedom (df) and the Breslow-Day equation (see Other Publications of Related Interest no.3). The effect of provider by treatment group on mortality and the interaction between provider and treatment group on outcome were assessed using an analysis of proportions with the weighted least squares method. In addition, sensitivity analyses were performed including only high quality trials, and excluding one paramedic trial.

Results of the review
Six randomised placebo-controlled trials (RCTs) with 6,434 patients and three follow-up studies were included.

Quality assessment. Scores ranged from 0.43 to 0.91 from a maximum possible score of 1. Three RCTs scored 0.78 or more. The majority of studies failed to report concealment of allocation and blinding of outcome assessment.

Homogeneity There was no evidence of heterogeneity for short-term hospital mortality (P = 0.9 and plot of mortality for prehospital vs in-hospital thrombolysis showed consistency between outcomes) or for 2-year mortality (P = 0.86). Homogeneity was poor for 1-year mortality (P = 0.4). Mortality. Overall short-term hospital mortality (six RCTs): prehospital thrombolysis significantly reduced short-term mortality. Pooled OR = 0.83 (95% CI: 0.70, 0.98; P = 0.03). Data were insufficient to evaluate mortality at 30 days and 60 days. 1-year mortality (two RCTs): no significant difference between prehospital and in-hospital thrombolysis. Pooled OR = 0.68 (95% CI: 0.26, 1.80; P = 0.44). 2-year mortality (two RCTs): no significant difference between prehospital and in-hospital thrombolysis. Pooled OR = 1.18 (95% CI: 0.62, 2.22; P = 0.62). 5-year mortality (one RCT): significantly higher mean survival in the prehospital thrombolysis group. Difference 208 days (95% CI: 42, 374; P < 0.03). Secondary outcomes: these were defined inconsistently and variably reported. Sensitivity analysis. Analysis limited to higher quality trials (three RCTs): results were similar to overall results with pooled OR = 0.84 (95% CI: 0.70, 0.99). Influence of provider qualifications: assessed by considering only studies of mobile intensive care units with administration by intensive care physician (four RCTs): results were similar to overall results with pooled OR = 0.80 (95% CI: 0.72, 1.02). Provider by treatment group effect: this was not significant (P = 0.16). Provider on mortality effect: this was not significant (P = 0.58). Time to thrombolysis treatment. Prehospital thrombolysis significantly improved time to needle for thrombolysis: the time difference and standard error (SE) to thrombolysis between the prehospital group (104 minutes, SE = 7) and the in-hospital group (162 minutes, SE = 16) was 60 minutes (P = 0.007). Re-analysis after exclusion of one study set in towns and villages at distances that compromised transfer time: the time difference to thrombolysis between the prehospital group (104.67 minutes) and the in-hospital group (149.33 minutes) was 45 minutes (P = 0.01).

Authors’ conclusions
Prehospital thrombolysis for AMI significantly decreases the time to thrombolysis and all-cause hospital mortality.

CRD commentary
The aims were stated and inclusion criteria defined in terms of study design, participants, intervention and outcomes. The process of study selection was described and inter reviewers agreement levels reported. Several sources were searched and attempts were made to locate unpublished studies, though it was not stated whether any language restrictions were applied. The methods used to assess and score validity were described. Relevant details of the included studies were presented in tabular format. Heterogeneity was discussed and assessed statistically and results were pooled where appropriate. Sensitivity analysis was performed to investigate the influence of various factors, including study...
validity, on the results. This thorough review was clearly written and presented. Evidence supports the authors’ conclusions.

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

Practice: The authors state that there is sufficient evidence to suggest that prehospital thrombolysis reduces the delay to treatment in settings with long transit times, and that the choice of thrombolytic agent remains less important than making the correct diagnosis and rapid and safe administration of the thrombolytic agent.

Research: The authors state that in urban settings with relatively short transit times, prehospital thrombolysis should be evaluated in comparison with 12-lead ECG interpretations with advance notification and rapid transportation to definitive care.

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the reliability of the review and the conclusions drawn.