Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour

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Authors' objectives
To determine the relation between benefit from fibrinolytic therapy and treatment delay (time between onset of symptoms and treatment) for mortality from myocardial infarction (MI).

Searching
MEDLINE was searched from 1983 to 1993.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of fibrinolytic therapy versus placebo or control, which included at least 100 patients, were included.

Specific interventions included in the review
Fibrinolytic therapy.

Participants included in the review
Patients with suspected MI were included.

Outcomes assessed in the review
The outcome assessed was the short-term mortality, defined as being up to 35 days post-event.

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 authors performed the selection.

Assessment of study quality
The authors do not report the criteria used to assess validity, or how the validity assessment was performed.

Data extraction
The authors do not state how the data were extracted for review, or how many of the authors performed the data extraction. The following data were extracted from the primary studies: time from symptom onset till fibrinolytic therapy was received, and short-term mortality. Mortality observations of the separate trials were positioned at the average treatment delay if reported, and otherwise at the mid-point of the described time-window. Patients were allocated to 6 subgroups according to treatment delay. Absolute and relative mortality effects were calculated in each of these categories. The absolute mortality reduction plus its standard deviation (SD) and 95% confidence intervals (CIs) were calculated as the difference in the percentage dying in the fibrinolytic group and the controls. The odds ratios (ORs) of the proportional effect of fibrinolytic therapy on 35-day mortality according to treatment delay, were calculated. The number-needed-to-treat (NNT) to save one additional life within 35 days was calculated for each time period.

Methods of synthesis
How were the studies combined?
Linear and non-linear regression functions were fitted to the data from the separate trials, with the data being weighted by the inverse of the variance of the absolute benefit.
How were differences between studies investigated?
The Breslow-Day test was used to investigate differences between studies.

Sensitivity analysis was performed: (1) by reanalysing the data after excluding 2 trials where the indications for fibrinolytic therapy may not have been appropriate; (2) after excluding the intra-coronary studies; and (3) after including only trials with at least 1000, 500 or 250 patients.

Results of the review
Data from 22 RCTs (N=50,246) were included in the regression analysis.

Data from 11 RCTs were included in the calculation of the NNT per treatment delay period.

The number of patients randomised within 2 hours of symptom onset was 5,762; 10,435 patients were randomised within 2 to 3 hours of symptom onset.

The absolute mortality reductions per 1000 treated patients were, for patients who presented:

Within 1 hour of symptom onset, 65 lives saved (SD 14, 95% CI: 38, 93); NNT 15.
In second hour after symptom onset, 37 lives saved (SD 9, 95% CI: 20, 55); NNT 27.
Two to 3 hours after symptom onset, 26 lives saved (SD 6, 95% CI: 14, 37); NNT 38.
Three to 6 hours after symptom onset, 29 lives saved (SD 5, 95% CI: 19, 40); NNT 34.
Six to 12 hours after symptom onset, 18 lives saved (SD 6, 95% CI: 7, 29); NNT 56.

The ORs were significantly different over the 6 treatment delay periods (Breslow-Day test, P=0.001.

The proportionate mortality reductions were 48% (95% CI: 31, 61) for patients treated within 1 hour, 44% (95% CI: 32, 53) for those treated within 2 hours, and 20% (95% CI: 15, 25) for those treated later.

The best-fit regression model (correlation, $R^2=0.32$) was found to be: absolute benefit per 1000 treated patients equals $19.4 - 0.6 \times $ (treatment delay in hours) plus 29.3 (treatment delay in hours) minus 1.

The above findings were not changed after the sensitivity analysis.

Cost information
None. The financial costs of implementing earlier thrombolysis are mentioned in a comment on the review.

Authors' conclusions
The beneficial effect of fibrinolytic therapy is substantially higher in patients presenting within 2 hours after symptom onset, compared to those presenting later. Avoidance of unnecessary treatment delay should be given top priority so as to improve the survival prospects of patients with suspected evolving MI.

CRD commentary
This is a clearly-written review. Limiting the literature search to one database may have resulted in the omission of some relevant studies. Details of the included studies are lacking, of relevance would have been the following: patients' characteristics, inclusion and exclusion criteria for patients, definitions of terms such as 'evolving' or 'suspected' MI, the fibrinolytic regime used, the methods used to estimate treatment delay time, and an evaluation of the quality of the
primary studies according to defined criteria. As the authors correctly state, there may be sources of bias in the review such as differences in the baseline characteristics between time-to-treatment groups, the unknown delay between randomisation and actual initiation of therapy, and the individual delays within studies. It is not possible to comment on the generalisability of the results given the limited literature search and the lack of validity criteria applied to the primary studies.

**Implications of the review for practice and research**
A systematic review, which includes an extensive literature search and an evaluation of the quality of the primary studies, is required to investigate the relationship between benefit from fibrinolytic therapy and treatment delay.

**Bibliographic details**

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**Other publications of related interest**

This additional published commentary may also be of interest. Redfern C. Meta-analysis: mortality is reduced when fibrinolytic therapy is started soon after the onset of MI symptoms. ACP J Club 1997;126:31.

**Indexing Status**
Subject indexing assigned by NLM

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**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.