

## Articles

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

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## Summary

**Background** There is conclusive evidence from clinical trials that reduction of mortality by fibrinolytic therapy in acute myocardial infarction is related to the time elapsing between onset of symptoms and commencement of treatment. However, the exact pattern of this relation continues to be debated. This paper discusses whether or not appreciable additional gain can be achieved with very early treatment.

**Methods** The relation between treatment delay and short-term mortality (up to 35 days) was evaluated using tabulated data from all randomised trials of at least 100 patients ( $n=22$ ; 50 246 patients) that compared fibrinolytic therapy with placebo or control, reported between 1983 and 1993.

**Findings** Benefit of fibrinolytic therapy was 65 (SD 14), 37 (9), 26 (6) and 29 (5) lives saved per 1000 treated patients in the 0–1, 1–2, 2–3, and 3–6 h intervals, respectively. Proportional mortality reduction was significantly higher in patients treated within 2 h compared to those treated later (44% [95% CI 32, 53] vs 20% [15, 25];  $p=0.001$ ). The relation between treatment delay and mortality reduction per 1000 treated patients was expressed significantly better by a non-linear ( $19.4-0.6x+29.3x^{-1}$ ) than a linear ( $34.7-1.6x$ ) regression equation ( $p=0.03$ ).

**Interpretation** The beneficial effect of fibrinolytic therapy is substantially higher in patients presenting within 2 h after symptom onset compared to those presenting later.

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## Introduction

The reduction in mortality that can be achieved with reperfusion therapy in patients with evolving myocardial infarction depends on the time elapsing between onset of symptoms and initiation of treatment or, more specifically, on the duration of coronary occlusion before reperfusion.<sup>1</sup> Although earlier reperfusion yields a better clinical outcome the relation between treatment delay and mortality reduction is controversial. A key question is whether or not a substantial additional reduction of the mortality risk can be achieved with very early treatment, ie, within 2–3 h after onset of symptoms. The concept of a 'first golden hour'<sup>2</sup> is supported both by experimental studies and randomised trials comparing pre-hospital with in-hospital therapy.<sup>2,3</sup> By contrast, the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group, in a pooled dataset of randomised trials of more than 1000 patients,<sup>4</sup> reported only a gradual decrease of benefit with longer delay. We present an alternative analysis of data from previous trials.

## Experimental studies

The duration of coronary occlusion and the extent of collateral circulation are the main determinants of infarct size in pigs, dogs, cats, and other animals.<sup>5–7</sup> In animals with a coronary collateral circulation similar to that of humans an occlusion persisting for 15–30 min generally does not lead to significant myocardial damage.<sup>6,7</sup> Thus, necrosis can be prevented provided reperfusion is achieved within this period.<sup>8</sup> A small area of necrosis usually occurs with reperfusion after 45 min occlusion, while the mid-endocardial and subendocardial zones are still viable.<sup>6</sup> Longer durations of coronary occlusion result in progressive growth of the infarction and reduction of the amount of salvageable myocardium. At 90 min the extent of cell death involves 40–50% of the area at risk; less than half of the jeopardised myocardium remains viable at that time.<sup>3,6</sup> 6 h after the onset of continuous ischaemia the area at risk is fully infarcted such that myocardial salvage will be minimal.

In humans, the thrombotic event frequently consists of multiple cycles of temporary occlusion and reperfusion. The degree of chest pain (if present) varies among patients so that it is often difficult to determine the exact duration of the coronary occlusion. Nevertheless, data indicate that evolution of (enzymatically detectable) infarct size over time in humans shows a pattern similar to that in animals.<sup>9</sup>

## Pre-hospital versus in-hospital thrombolysis

Various clinical trials have shown that early restoration of coronary patency improves survival.<sup>10–13</sup> Later recanalisation may also be beneficial, particularly in patients with sufficient collateral flow and in those with stuttering infarction. Randomised trials comparing pre-

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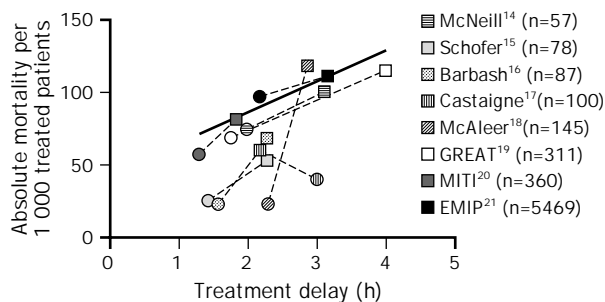


Figure 1: Mortality at 35 days in randomised studies comparing prehospital (circles) with in-hospital (squares) thrombolytic therapy

All trials (except that of Castaigne) showed trend favouring prehospital thrombolysis. Regression line (bold, weighted by number of patients included in mortality result) was mainly determined by EMIP study.

hospital with in-hospital therapy<sup>14-21</sup> have shown a substantial beneficial effect of very early thrombolytic therapy. Although these studies were too small to show statistical significance, such significance was reached in pooled analyses of the data.<sup>2,22</sup> The largest EMIP trial, with 5469 randomised patients, reported 15 (SD 8) additional patients alive at 30 days per 1000 patients as a result of 1 h earlier treatment.<sup>21</sup> Figure 1 shows the weighted regression line of all eight randomised studies.<sup>14-21</sup> In these studies, the average delay from symptom onset to initiation of therapy was 2.1 h in the prehospital patients and 3.1 h in the in-hospital patients. 1 h earlier treatment within 3 h from symptom onset is associated with a benefit of 21 (6) lives per 1000 treated (p=0.002).

#### FTT analysis

The Fibrinolytic Therapy Trialists' Collaborative Group presented a systematic analysis of the pooled data from all unconfounded trials of fibrinolytic therapy *versus* control or placebo that randomised at least 1000 patients with suspected myocardial infarction.<sup>4</sup> Nine trials were included with 58 600 patients, among whom 6177 deaths (10.5%) were reported within 35 days. The effect of treatment on mortality and morbidity was studied in various patient categories. One of the FTT subanalyses described the benefits of fibrinolytic therapy in five subgroups according to the delay from symptom onset to randomisation (0-1,  $\geq 1-3$ ,  $\geq 3-6$ ,  $\geq 6-12$  and  $\geq 12-24$  h). Mortality reduction was highest among patients presenting in hospital within 1 h: the absolute benefit was 35 (11) additional patients alive per 1000 treated. In patients presenting  $\geq 1-3$  and  $\geq 3-6$  h the benefits were 25 (5) and 19 (5) additional alive patients per 1000 treated, respectively.

In patients with ST elevation or bundle branch block (n=45 000, 77% of the population) the absolute effects of fibrinolytic therapy were slightly larger. Benefits per 1000 treated patients were 39 (12), 30 (5), 27 (6), 21 (7), and 7 (7) in the respective subgroups. The relation between these benefits and the average delay from symptom onset (0.98, 2.50, 4.79, 9.11, and 17.48 h, respectively) was described as a straight regression line. Every additional hour of treatment delay from onset of symptoms was associated with a reduction in benefit by approximately 1.6 (0.6) lives per 1000 patients.

The FTT investigators concluded from these data a gradually increasing benefit with earlier treatment, without significant additional treatment effect at 0-1 h. According

to this analysis little would be gained by extra efforts to achieve very early, prehospital, therapy.

#### Alternative presentation of trial data

Since the FTT analysis is at variance with the experimental data, and with the larger benefit found in direct, randomised comparison of prehospital with in-hospital therapy, an alternative presentation of the trial data seems appropriate. Furthermore, estimations of benefit for early treatment in the FTT analysis may have been influenced by the chosen framework for analysis.

The inclusion-threshold of 1000 patients for each of the nine studies included in the FTT analysis is rather arbitrary. There is no good reason to exclude smaller trials. Although the number of patients in the smaller studies may not be sufficient to prove the effect of thrombolytic therapy, these studies may nevertheless assist a more powerful estimation of treatment effects in subgroups of patients in a pooled dataset; more so, because several smaller studies excluded from the FTT analysis included a significant proportion of patients who were treated very early.

The statistical analysis was based on subdivision of patients according to delay from symptom onset with only two benefit estimations in the first 3 h (at average delay times of 0.98 and 2.50 h, respectively). In this way, part of a potential large effect in the first 2 h may be obscured by a relatively small effect in the third hour. A more differentiated subdivision seems more appropriate to study the effect of very early therapy.<sup>23</sup> Furthermore, non-linear models might be developed and tested in addition to the linear FTT model.

#### Methods

For the reasons given, we studied the delay/benefit relation in a modified dataset, covering all randomised trials of fibrinolytic therapy *versus* placebo or control which included at least 100 patients. These trials were reported between 1983 and 1993 and indexed in the MEDLINE information system.<sup>24</sup> There are 22 such trials.<sup>12,13,25-44</sup> The indication for fibrinolytic therapy in two of the trials may not have been appropriate: the USIM trial included a high proportion (32%) of patients with unstable angina, and the ISIS-3 uncertain indication group consisted of patients without or with only minor ST elevation;<sup>43,44</sup> these patient subgroups are unlikely to benefit from fibrinolysis.<sup>45-47</sup> The USIM and ISIS-3 trials included 4250 patients who were treated within 3 h of symptom onset and may therefore seriously bias benefit estimations for early treatment of those with confirmed infarction. Accordingly, we analysed data from previous trials both with and without inclusion of USIM and the ISIS-3 uncertain indication group.

Tabulated data were collected on time from symptom onset and short-term mortality (up to 35 days). 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. The data of 11 trials were sufficiently detailed to be split into different time intervals.<sup>12,13,27,29,31-33,41-44</sup> Patients were subsequently allocated to six subgroups according to treatment delay (0-1,  $\geq 1-2$ ,  $\geq 2-3$ ,  $\geq 3-6$ ,  $\geq 6-12$ , and  $\geq 12-24$  h from symptom onset to randomisation). Absolute and relative mortality effects of fibrinolytic therapy were evaluated in each of these categories. USIM and ISIS-3 uncertain indication patients were excluded from this analysis.

Benefit was defined as the absolute mortality reduction, calculated as the difference in the percentage dying in the fibrinolytic group and the controls (we also calculated the SD and 95% CI of this difference). Linear ( $\alpha+\beta x$ ) and non-linear ( $\alpha+\beta x+\gamma x^2$  and  $\alpha+\beta x+\gamma x^{-1}$ ) regression analyses were performed to determine the relation between benefit and treatment delay.

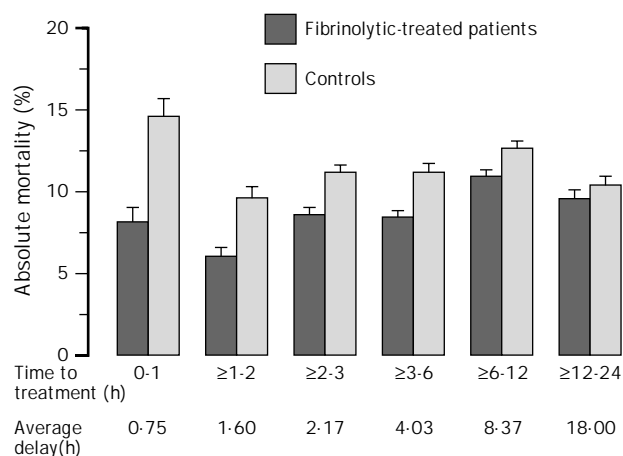


Figure 2: Mortality at 35 days among fibrinolytic-treated and control patients, according to treatment delay

Regression functions were fitted in the tabulated data from the separate trials. Data were weighted by the inverse of the variance of the absolute benefit described.<sup>4</sup> Goodness of fit was expressed as the ratio of regression sum of squares and total sum of squares ( $R^2$ -value). Regression analyses were performed both with and without USIM and ISIS-3 uncertain indication data.

## Results

The 22 trials included a total of 50 246 patients, of whom 5762 (11%) were randomised within 2 h of symptom onset and another 10 435 (21%) between 2 and 3 h. Fibrinolytic therapy appeared to be beneficial up to at least 12 h (figure 2). The absolute reduction in mortality was greatest among patients who presented within 1 h of symptom onset (average delay 0.75 h). Benefit in this group was estimated at 65 (SD 14; 95% CI 38, 93) lives saved per 1000 treated patients, which is higher than the FTT estimation of benefit at nearly the same time point (0.98 h) of 35 (11). Benefit was also higher in our analysis than in the FTT analysis among patients randomised in the second hour (37 [9]; 20, 55) per 1000 treated. The

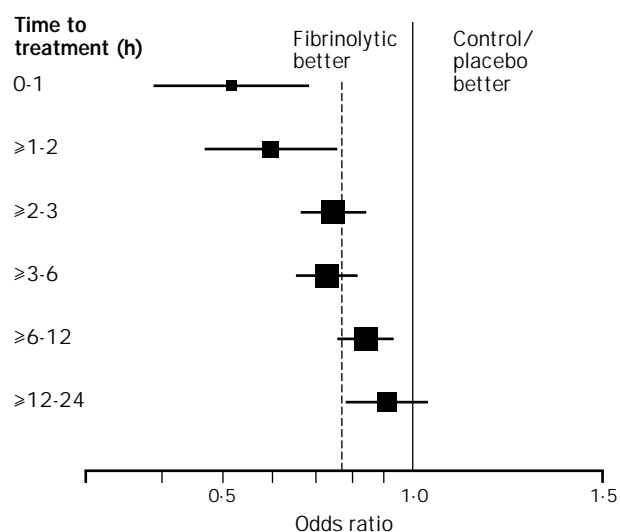


Figure 3: Proportional effect of fibrinolytic therapy on 35-day mortality according to treatment delay

Odds ratios, plotted with 95% CI on a log scale, are significantly different over the six groups (Breslow-Day test,  $p=0.001$ ). Areas of black squares proportional to amount of statistical information

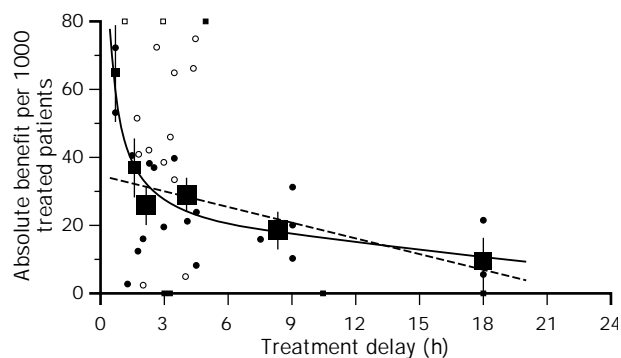


Figure 4: Absolute 35-day mortality reduction versus treatment delay

Small closed dots: information from trials included in FTT analysis; open dots: information from additional trials; small squares: data beyond scale of x/y cross. The linear ( $34.7-1.6x$ ) and non-linear ( $19.4-0.6x+29.3x^{-1}$ ) regression lines are fitted within these data, weighted by inverse of the variance of the absolute benefit in each datapoint.<sup>4</sup> Black squares: average effects in six time-to-treatment groups (areas of squares inversely proportional to variance of absolute benefit described).

benefit per 1000 treated in the subgroups presenting at  $\geq 2-3$  h,  $\geq 3-6$  h,  $\geq 6-12$  h, and  $\geq 12-24$  h was respectively 26 (6; 14, 37), 29 (5; 19, 40), 18 (6; 7, 29), and 9 (7; -5, 22).

Similarly, the proportional mortality reduction was highest in the 1 h patients (48% [95% CI 31, 61]; figure 3), and significantly higher in patients treated within 2 h than in those treated later (44% [32, 53] and 20% [15, 25], respectively). By contrast with the FTT report, odds ratios differed significantly over the time-to-treatment groups ( $p=0.001$ , figure 3).

The relation between absolute benefit of fibrinolytic therapy and treatment delay can be described by a linear function, similar to FTT, which shows a significant reduction in benefit of approximately 1.6 (0.5) lives per 1000 patients per hour of treatment delay ( $H_0: \beta=0$  rejected;  $p<0.01$ ;  $R^2=0.22$ ). This linear model was not significantly improved by addition of the term  $\gamma x^2$  ( $H_0: \gamma=0$  not rejected;  $p=0.29$ ;  $R^2=0.25$ ). However, the component  $\gamma x^{-1}$  of the second non-linear model had a significant contribution to the regression function ( $H_0: \gamma=0$  rejected;  $p=0.03$ ). In fact, this latter model fits best with the data ( $R^2=0.32$ ), in particular with the early observations (figure 4). Inclusion of the USIM and ISIS-3 uncertain indication data and exclusion of the intracoronary studies (WWashICy<sup>26</sup> and ICINy<sup>28</sup>) did not essentially change these findings. Further analyses were performed including all trials with at least 1000 (FTT dataset), 500 and 250 patients, respectively. In all cases, the second non-linear model was significantly better than the linear model.

## Discussion

In animals with a coronary circulation similar to that of humans, the amount of myocardial tissue that is salvageable directly depends on the duration of coronary occlusion. This dependency is non-linear. Very early reperfusion of the occluded coronary artery (within 30 min) may lead to full recovery of ischaemic tissue and thus prevent necrosis. In experimental models most of the irreversible damage to the myocardium occurs between 1 and 2 h, after the occlusion, and little or no salvage can be achieved after 6 h of occlusion.

These findings correspond very well with the relation between infarct size estimated by assay of cardiac enzymes and the delay in thrombolytic treatment, as measured in 1334 patients with evolving myocardial infarction.<sup>9</sup> The cumulative release of myocardial  $\alpha$ -hydroxybutyrate dehydrogenase during the first 72 h after infarction ( $Q_{72}$ ) was comparatively small in patients treated within 1 h from onset of symptoms. A very steep increase in the rate of enzyme release was noted between 1 and 2 h of treatment delay (the increase was relatively small thereafter). The life-saving effect of very early reperfusion therapy has been supported by pooled analyses of studies which randomised between immediate, prehospital initiation of therapy and delayed, in-hospital therapy (figure 1).<sup>2,22</sup>

This advantage of very early therapy in the prehospital studies is much larger than the effect of 1 h earlier treatment reported by the FTT investigators (1.6 lives per 1000 treated), who compared in-hospital thrombolytic with placebo or conventional therapy.<sup>4</sup> We emphasise that patients with a short treatment delay tend to differ from those who wait longer before seeking medical help: many of the patients with very large infarcts (with the highest mortality risk and greatest treatment benefit)<sup>48</sup> report early, whereas elderly patients tend to wait longer.<sup>49,50</sup> Therefore, the randomised comparisons of earlier versus later therapy may provide better estimates of the delay/effect relation than comparison of different cohorts from the large randomised trials. Furthermore, the formal statistical approach has a major influence on the results of the FTT analysis. Results from previous investigations indicating a non-linear delay/benefit relation (eg, the GISSI-1 clinical trial<sup>12</sup>) were considered hypothesis-generating, whereas the outcomes of experimental and prehospital trials were dismissed.<sup>4</sup> In the combined trial data (summarised by five datapoints) no significant deviation of linearity was observed and thus the hypothesis of a linear delay/benefit relation was not rejected in the FTT analysis. By contrast, our alternative analysis supports a non-linear relation which is in agreement with the experimental and prehospital data (figure 4). A large reduction in mortality was detected in patients treated within 1 h of symptom onset (65 [14] per 1000 treated). The decrease in benefit in the 0.75–1.6 h interval (51 min) was roughly 33 lives per 1000 treated per hour (from 65 [14] to 37 [9]), and declined rapidly to about 3.3 lives per h in the 1.6–4.0 h interval (from 37 [9] to 29 [5]), and only 1.4 lives per h after this period (from 29 [5] at 4.0 h to 9 [7] at 18.0 h). The delay/benefit relation could be significantly better described by a non-linear ( $\alpha + \beta x + \gamma x^{-1}$ ) rather than a linear ( $\alpha + \beta x$ ) function. Although the goodness of fit within the tabulated data of the separate trials remains limited ( $R^2=0.32$ ), the non-linear function does fit very well with the benefit estimations in the six time-to-treatment groups (figure 4).

The concept of a first golden hour in myocardial infarction is supported by our analysis, although our estimations may be biased by differences in baseline characteristics between time-to-treatment groups, the unknown delay between randomisation and actual initiation of therapy and coronary reperfusion, and the unknown individual delays within the reported studies. The benefit of thrombolytic therapy initiated within 30–60 min after onset of symptoms can be estimated at 60–80 additional patients alive at 1 month per 1000 treated compared with conventional therapy. The benefit

of therapy within 1–3 h is in the range 30–50 per 1000 treated.

From a clinical standpoint, the challenge is to initiate fibrinolytic treatment within the first 2 to 3 h after symptom onset. A first important step will be to increase public awareness of the need to reduce delay in seeking medical help for cardiac symptoms. Second, as an aid to rapid diagnosis when there is chest pain suggestive of infarction, the general practitioner or ambulance team should obtain—preferably on-site—a computer-interpreted standard 12-lead ECG.<sup>51</sup> With certainty of diagnosis, thrombolytic therapy may be started quickly, before hospital admission. Patients in whom myocardial infarction cannot be confirmed on site, and those presenting directly to the emergency department, may still benefit from emergency room initiation of thrombolytic infusion. Avoidance of unnecessary treatment delay should be given top priority so as to improve the survival prospects of patients with suspected evolving myocardial infarction.<sup>52</sup>

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