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Clinical Perspectives

Selection of reperfusion therapy for individual patients with evolving myocardial infarction

Introduction

The overall benefits of reperfusion therapy for acute myocardial infarction have been established unequivocally. Physicians can now choose among different thrombolytic regimens based on streptokinase and tissue plasminogen activator, while other regimens are under development (for example reteplase and saruplase). In some hospitals, direct angioplasty is an alternative.

Key questions in clinical practice are how widely should thrombolytic therapy be used, and whether different reperfusion strategies should be chosen for different types of patients and in different clinical circumstances. This is even more of an issue when medical resources are limited. Such decisions could be based on simple univariate criteria (older vs younger patients, anterior vs inferior infarction) or on more complex multivariate modelling. Moreover, some consideration of the cost/effectiveness, the relative safety and the complexity (e.g. primary angioplasty) of different therapeutic options need to be taken into account.

On 20 and 21 February 1995, a colloquium involving several groups of investigators was organised to review these issues (Appendix). Prior to the meeting, several questions were posed to guide the discussion and to attempt to obtain consensus:

1. Reperfusion therapy preserves viable myocardial tissue and reduces mortality in acute myocardial infarction patients. Are left ventricular ejection fraction and infarct size adequate 'surrogate' measures for the effects on mortality and morbidity?
2. Mortality with or without reperfusion therapy can be predicted by individual characteristics. What are the short-term effects of reperfusion therapy in different subgroups of patients?
3. Improved survival with reperfusion therapy is sustained after the first year. What are the determinants of the long-term survival advantage after reperfusion therapy?
4. The mortality reduction produced by reperfusion therapy is related to the time from symptom onset to treatment. What is the nature of this relationship? Is there a first 'golden hour' after symptom onset in which treatment benefits are particularly large?
5. Do patients treated late after onset of symptoms — between 12 and 24 h — also benefit from reperfusion therapy?
6. A negative aspect of thrombolytic therapy is the possible occurrence of intracranial haemorrhage. What are the most important predictors of intracranial haemorrhage and excess of stroke with thrombolytic treatment?
7. Commonly used modes of reperfusion therapy in clinical practice include different thrombolytic regimens with streptokinase or (accelerated) tissue plasminogen activator, and direct angioplasty. What is the relationship between survival benefits, cerebral bleeding risks and costs for these three options?
8. How can the benefits, risks and costs of different reperfusion strategies be integrated into clinical decision making?

A summary of the discussion of each of these issues is provided in the following sections. Although there was a consensus on most topics, in some areas agreement could not be reached and the alternative views are summarized. The occurrence of contrasting viewpoints can partly be explained by differences in emphasis on pathophysiological concepts and results of large trials. It should be appreciated, however, that these differences in interpretation do not lead to major differences in routine treatment strategies.

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1. Reperfusion therapy preserves viable myocardial tissue and reduces mortality in acute myocardial infarction patients. Are left ventricular ejection fraction and infarct size adequate 'surrogate' measures for the effects on mortality and morbidity?

Infarct size can be measured from the total quantity of enzymes or other proteins released from the

myocardium. Early reperfusion therapy results in rapid protein release[1,2]. The total quantity of proteins released (indicating infarct size) is reduced by 20% to 35% with thrombolytic therapy compared with control[1,3–5]. Similarly, more effective reperfusion therapy yielded smaller infarct size than standard therapy[6,7]. In patients with a first infarct, infarct size is inversely correlated with residual left ventricular function[7,8]. However, in most randomized controlled trials, differences in left ventricular ejection fraction between patients receiving reperfusion therapy and controls were small, although generally in favour of the treated group (pooled left ventricular ejection fraction 54% in treated patients vs 51% in controls)[9], whereas substantial survival benefits are demonstrated by large-scale randomized trials[10,11]. In the Fibrinolytic Therapy Trialists' (FTT) collaborative overview of the nine largest comparisons of thrombolytic therapy vs control, this benefit was estimated to be 30 fewer deaths per 1000 patients with ST elevation or bundle branch block treated within about 6 h from symptom onset[12].

Physiological studies might heighten our understanding of the possible mechanisms of action of thrombolytic treatment — for example, the relationship between *early* coronary patency (TIMI-3 flow in the infarct related artery) and infarct size. Moreover, several studies have documented a close relationship between infarct size, residual left ventricular function, coronary patency and long-term survival[13,14]. Although studies measuring early coronary patency, enzymatic infarct size and ventricular function may give an indication of the effect of (new) reperfusion strategies, such studies cannot reliably determine the net clinical benefit of reperfusion therapy. Survival after myocardial infarction depends not only on early patency but also on *sustained* coronary patency and the healing process of the infarction. Furthermore, the *risk* of intracranial haemorrhage with treatment is largely independent of infarct size and left ventricular ejection fraction. Hence, determination of the balance between survival benefit and cerebral bleeding risk with different treatment strategies requires large mortality trials.

Conclusions

- Coronary artery patency, left ventricular ejection fraction and infarct size (as determined by cumulative myocardial protein release) can be used to make initial assumptions of the efficacy of reperfusion regimens.
- Subsequently, large mortality trials are required to assess reliably the survival benefits and bleeding risks of reperfusion strategies.

2. Mortality with or without reperfusion therapy can be predicted by individual characteristics. What are the short-term effects of reperfusion therapy in different subgroups of patients?

Several studies have shown that the risk of death from acute myocardial infarction can be predicted at the time of hospital admission[15–21]. Some determinants of mortality cannot be altered by thrombolytic therapy, such as sex, age, baseline left ventricular function, a history of infarction and location of the current infarct[18]. The area of myocardium at risk can be estimated from total ST elevation on the presenting ECG and Killip class. Infarct size, as a proportion of the area at risk, can be influenced by reperfusion therapy, with greater salvage by earlier treatment. Thrombolytic therapy has been shown to improve survival in patients presenting with either ST elevation or bundle branch block within 12 h of symptom onset[12]. In an overview of the large trials there was no significant heterogeneity between the proportional mortality reductions in the different subgroups of patients studied. Consequently, the absolute number of deaths avoided by thrombolytic treatment appears to be greater in those groups with a higher mortality risk. Moreover, there was no support for withholding thrombolytic therapy on the basis of age alone as the survival advantages were similar in young and old: 15 (SD 4) lives saved per 1000 treated aged <55 years, 21 (SD 5) aged 55–64, 37 (SD 6) aged 65–74 and 13 (SD 14) aged ≥75 years, respectively. It should be appreciated, however, that the estimate of benefit in patients aged 75 years or over is imprecise due to the relatively small number of patients, and thus additional information from controlled trials would be valuable.

It is less clear whether there are worthwhile benefits among patients presenting with ST depression but without ST elevation or bundle branch block. Some of these patients have coronary occlusion and evolving posterior infarction and are at high risk of death, and so may well benefit from thrombolytic therapy. Others may be suffering from unstable angina pectoris, with extensive ischaemia but without occlusion of a major coronary artery, although a significant (non-occluding) stenosis may be present. In these patients, coronary angiography and coronary angioplasty or bypass surgery are often indicated, but thrombolytic therapy is less likely to be useful. Further trials are warranted to identify patients with ST depression who do benefit from early reperfusion therapy.

Another, not completely understood, phenomenon is the excess of deaths in thrombolytic treated patients on the first day, particularly in patients treated relatively late after onset of symptoms[12]. If there is a physiological reason for this early hazard which could be prevented then the benefits of thrombolytic therapy might be increased substantially.

Conclusions

- Almost all patients with evolving myocardial infarction presenting with ST elevation or bundle branch block up to at least 12 h from symptom onset will benefit from thrombolytic therapy.
- The proportional improvement in short-term survival produced by reperfusion therapy is generally similar in different subgroups of patients. Consequently, in absolute terms, high-risk patients (e.g. older patients, those with a history of infarction, anterior location of the current infarct, extensive ST elevation or shock) may benefit most from such therapy.
- More information is needed to define more accurately the survival benefit in the very elderly (age 75 years or over), and in patients with ST segment depression on the presenting ECG without ST segment elevation.

3. Improved survival with reperfusion therapy is sustained after the first year. What are the determinants of the long-term survival advantage after reperfusion therapy?

Follow-up studies confirm that reperfusion therapy provides sustained survival benefit at 4, 5 and 10 years[14,18,23,24]. In ISIS-2, streptokinase produced an absolute improvement in survival at 35 days of 29 (SD 5) fewer deaths per 1000 treated patients, while the absolute benefit was 28 (SD 7) fewer deaths per 1000 at 4 years. Hence, following the large divergence in survival during days 0–35, there was no significant divergence or convergence thereafter. The absolute benefit at 4 years among patients randomized within 0–3 and 4–6 h of symptoms onset (48 [SD 13] and 18 [SD 12], respectively) were similar to those at day 35 (44 [SD 9] and 25 [SD 8]). The greater absolute benefits observed at one month in patients at higher risk of death were also sustained: for example, among patients presenting with anterior ST elevation there were 71 (SD 11) and 62 (SD 15) fewer deaths per 1000 at 35 days and 4 years, respectively. Other reports confirm these observations[14,18,24]. By multivariate analysis, long-term survival can be predicted from measurements at the time of hospital discharge including left ventricular function, enzymatic infarct size, number of diseased vessels, and TIMI perfusion grade[13,14,24]. When such information is included, the initial therapy (thrombolysis or conventional) appeared not to be an independent predictor of long-term outcome. Thus the benefits of reperfusion therapy are obtained early after initiation of therapy, and are maintained thereafter.

One reservation expressed about the use of thrombolytic therapy in elderly patients is that any short-term survival advantage might be only transitory because of the high underlying mortality. However, although 4-year survival among patients aged 70 years or over at entry into ISIS-2 was only about 50%, the absolute reduction in 4-year mortality with streptokinase was at least as great among these patients (45 [SD 19] lives saved per 1000) as among those aged less than 70 years (23 [SD 7] lives saved per 1000). Thus, long-term benefits of reperfusion therapy are also apparent in elderly patients.

Conclusions

- The absolute mortality reduction produced by reperfusion therapy is sustained after the first year, but there is no evidence that it increases with more prolonged follow-up.
- Multivariate analysis of large trial databases may give more insight into the underlying relationships between patient characteristics and the effects of thrombolytic therapy on early and long term survival.

4. The mortality reduction produced by reperfusion therapy is related to the time from symptom onset to treatment. What is the nature of this relationship? Is there a first 'golden hour' after symptom onset in which treatment benefits are particularly large?

All the participants agreed that the earlier reperfusion therapy is initiated, the larger the survival advantage[10–12,15,25]. There was disagreement, however, as to whether the benefits of treatment within the first hour after symptom onset are substantially greater (that is a 'golden hour') than slightly later treatment[25], or whether there is only a gradual diminution of benefits with later treatment[12].

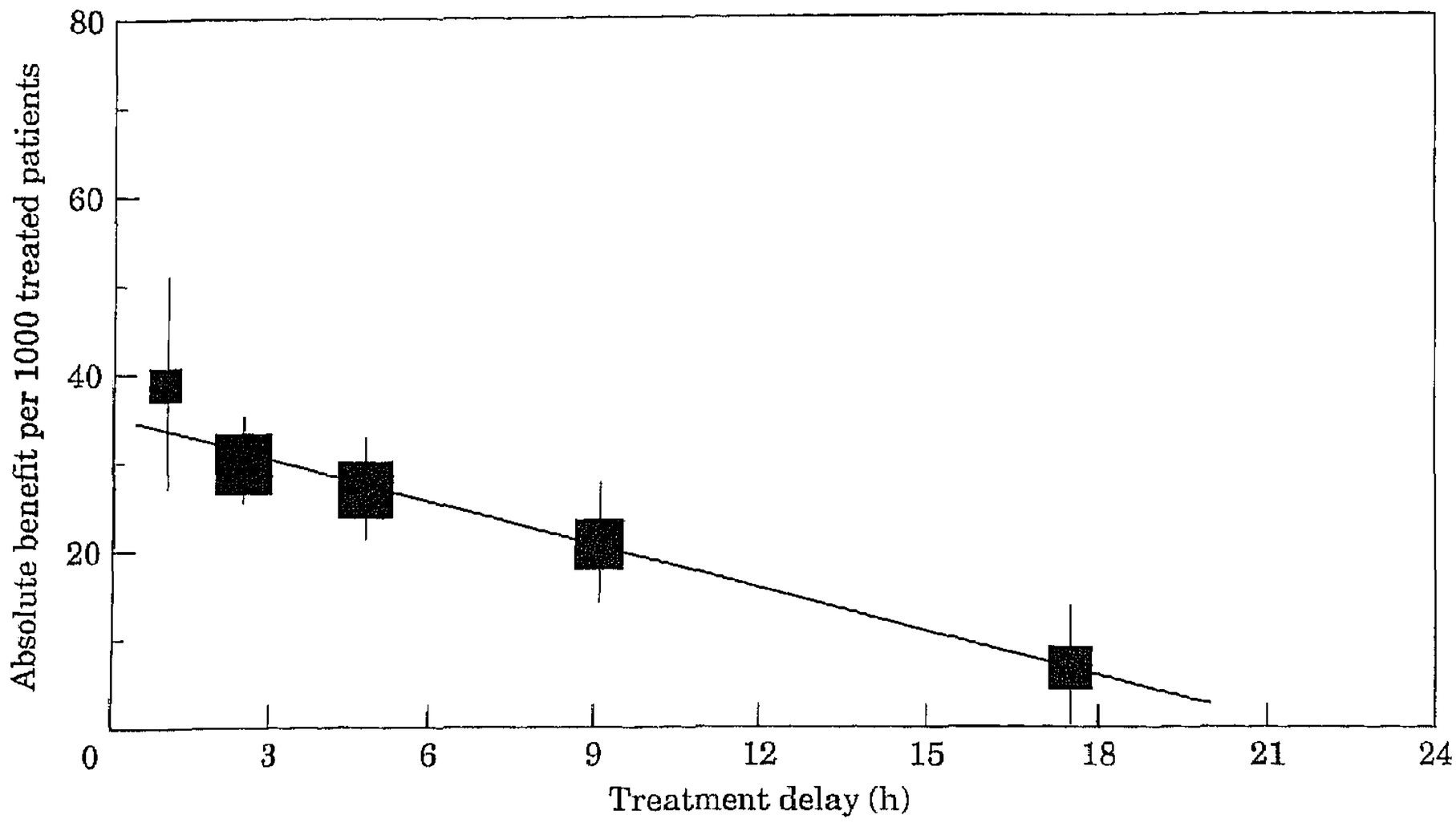

Figure 1 **Absolute reduction in 35-day mortality vs treatment delay as reported by the FTT investigators[1,2]. The loss of benefit per hour of delay to randomization was estimated at 1·6 (SD 0·6) per 1000 patients. The black squares represent the average effects in five time-to-treatment groups. The areas of these squares are inversely proportional to the variance of absolute benefit it describes.**

First viewpoint

One view was that although earlier thrombolytic treatment clearly produces greater benefit, the FTT overview of all relevant data from all nine trials that included more than 1000 patients (involving a total of 46 000 randomized patients) indicated that the decrease in the absolute benefit with increasing delay was fairly shallow, and was not significantly steeper in the first few hours than in subsequent hours (Fig. 1)[1,2]. A retrospective subgroup analysis of GISSI-1 had suggested that fibrinolytic therapy might be especially effective when started within 1 h from symptom onset, but this was not supported by the other large trials. Indeed, if GISSI-1 was excluded then the apparent benefit in those randomized in hours 0–1 was slightly below the sloping line in Fig. 1. Each hour of delay recorded among patients with ST elevation or bundle branch block was associated with a reduction in benefit of about 1·6 (SD 0·6) deaths per 1000 patients. This estimate may have been somewhat diluted by inaccuracies in assessing the delays, and so the real effect of each additional hour of delay may well be slightly greater, involving perhaps two (or even three) extra deaths per 1000, per hour. (The results of an analysis that included all smaller trials, i.e. at least 100 patients[35], may be biased because results for patients randomized within 0–1 h of symptom onset were not listed separately for several of these smaller trials, and those smaller trials that did report such information may have done so because their results were extreme.) In principle, the trials of pre-hospital vs in-hospital fibrinolytic therapy could provide directly randomized evidence of the relevance of an extra hour of delay, but even in aggregate they are far too small to measure reliably differences of only a few deaths per 1000, and their combined results are consistent with their being little or no improvement in outcome with slightly earlier treatment. Moreover, with respect to assessing the effects of very early treatment, the slight non-significant benefit of about 1 h earlier treatment in the largest trial (EMIP) was observed in those randomized 3–6 h after symptom onset, and not in those entered within 3 h[26].

Second viewpoint

In contrast to this first view, it was pointed out that an occlusion of less than 30 min in animals generally does not lead to irreversible myocardial damage[27–29], and small observational studies in humans support the plausibility of similar patterns[30,31]. Studies comparing pre-hospital and in-hospital therapy suggest a greater effect with earlier treatment[26,32,33]. For example, the largest study (EMIP) reported 15 fewer deaths per 1000 treated at a median of 2·2 h instead of 3·2 h after onset of symptoms (95% confidence limits: 27 fewer deaths to 1 additional death per 1000 treated, ns), albeit that most of this benefit was realised in patients treated between 3 and 6 h after onset of symptoms[26]. Although the pre-hospital trials were relatively small and the individual results

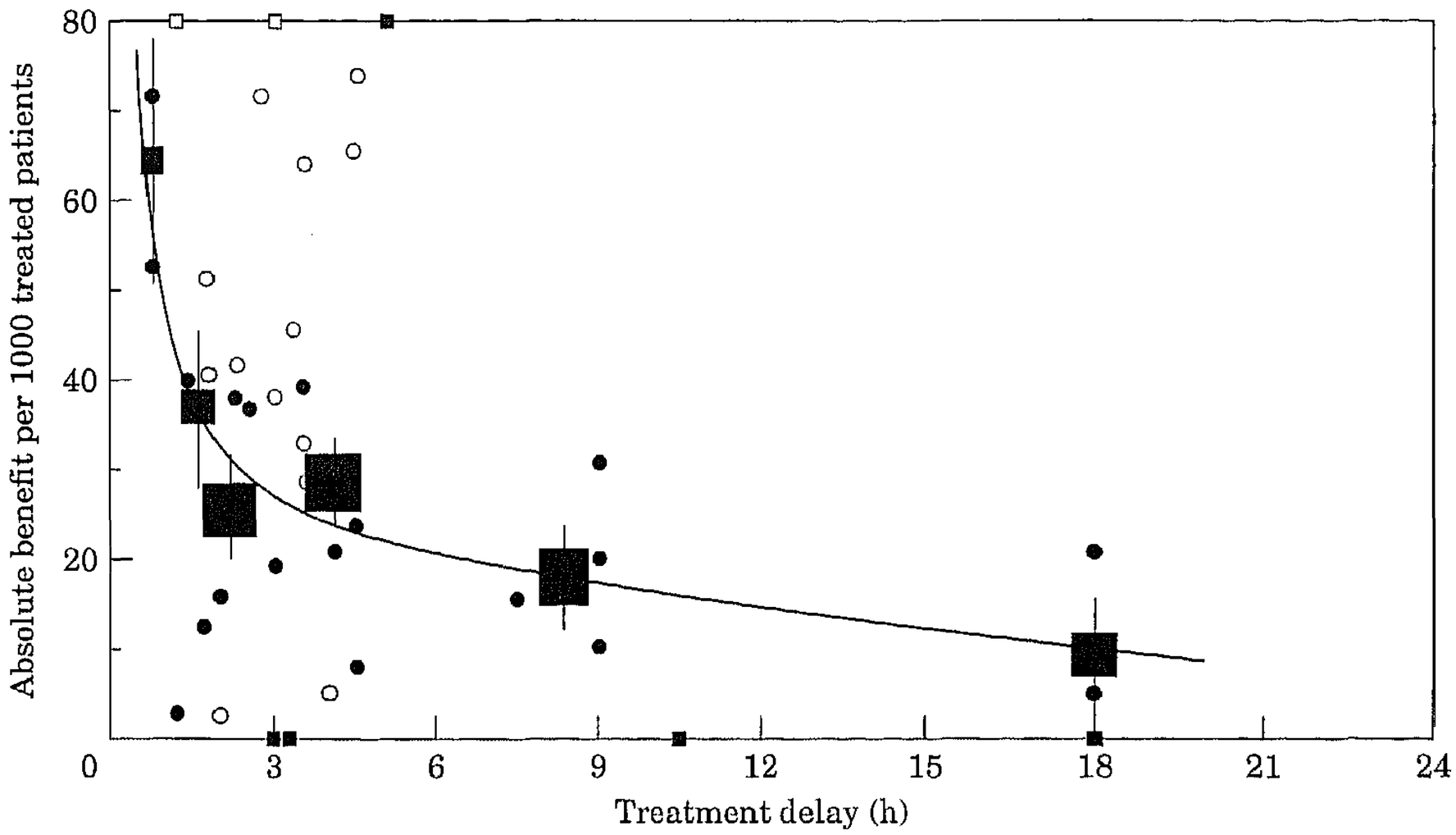

Figure 2 **Absolute 35-day mortality reduction vs treatment delay as reported by a re-analysis of the FTT data in combination with data from smaller trials (at least 100 patients) that randomized between fibrinolytic therapy and control or placebo[35]. The small closed dots represent information from trials included in the FTT analysis, the open dots represent information from additional trials. The small squares mark data beyond the scale of the y-axis. Linear (34·7–1·6x) and non-linear ($19{\cdot}4-0{\cdot}6x+29{\cdot}3x^{-1}$) regression lines are fitted within these data. The best fit was obtained with the non-linear mathematical function (significant contribution of the x^{-1}-component; largest R^2-value). The black squares represent the average effects in six time-to-treatment groups. The areas of these squares are inversely proportional to the variance of absolute benefit it describes.**

were not statistically significant, significance was reached in pooled analyses of the data[25,34].

The concept of a first 'golden hour' is supported by a re-analysis of the large trials in the FTT report in combination with data from smaller trials (at least 100 patients) that randomized patients between fibrinolytic therapy and control[35]. This analysis showed that the delay/benefit relationship could be significantly better described with a non-linear than with a linear function (see Fig. 2) The decrease in benefit up to approximately 1·5 h from symptom onset was about 30 lives per 1000 treated per hour, and declined rapidly to approximately three lives per hour in the 1·5–4·0 h interval and only 1·4 lives per hour after this period. Thus an extra effort to treat earlier (e.g. pre-hospital identification and therapy, and optimization of in-hospital logistics) will be particularly effective for patients reporting within the first hours after symptom onset, while some additional delay is less harmful in patients presenting late.

Conclusions

- It is clear that the earlier reperfusion therapy is started after the onset of symptoms, the larger the mortality reduction.
- There is no agreement as to the shape of the association between the mortality benefit and time from symptom onset to treatment for patients treated within the first few hours, and of the existence of a first 'golden hour'.

5. Do patients treated late after onset of symptoms — between 12 and 24 h — also benefit from reperfusion therapy?

Approximately 30% of patients with acute myocardial infarction arrive in hospital beyond the currently accepted time limit for reperfusion therapy, that is, more than 12 h from symptom onset[36]. Pharmacological or mechanical achievement of patency is possible in these late arrivals[37], and vessel patency may help to preserve left ventricular function or improve infarct healing and recovery, although significant myocardial salvage will probably not occur[38].

Overall, 7000 patients with ST elevation or bundle branch block presenting between 12 and 24 h from symptom onset have been randomized between fibrinolytic therapy and control[11,22,36,39]. Although the absolute benefit of seven (SD 7) fewer deaths per 1000 treated observed among these patients was

non-significant[12], benefit with earlier treatment and the gradual diminution of benefit with later treatment (see Figs 1 and 2) does suggest that worthwhile net benefits may await discovery among patients who present within 12 to 18 h or so after onset, especially if there are signs of ongoing ischaemia.

This suggestion is supported by subgroup observations in the LATE trial. Patients presenting after 12 h who were treated soon after admission, generally because of clear evidence of ischaemia, showed a 22% relative mortality reduction with tissue plasminogen activator[36]. In contrast, among those patients in whom the decision for therapy was delayed until an observational period of 3 h or longer, no beneficial effect was observed. Thus, patients presenting more than 12 h from symptom onset with clear indications of immediate thrombolytic therapy, i.e. ongoing chest pain or other signs of ongoing ischaemia (ECG), may benefit. Perhaps this is because some of these patients do not have continuous coronary occlusion, but rather intermittent occlusions — a 'stuttering infarction' — so that partial salvage of ischaemic myocardium may be achieved in them[40,41].

Conclusions

- Reperfusion therapy may be justified in patients with signs of ongoing ischaemia presenting between 12 and 24 h after symptom onset.
- Further study of the effect of reperfusion therapy in patients presenting late, and the mechanism of such effect, is needed.

6. A negative aspect of thrombolytic therapy is the possible occurrence of intracranial haemorrhage. What are the most important predictors of intracranial haemorrhage and excess stroke with thrombolytic treatment?

Intracranial haemorrhage is a rare event in patients with myocardial infarction receiving conventional therapy. Thrombolytic therapy does increase the rate of intracranial haemorrhage, despite attempts to avoid treating patients with an increased bleeding risk (particularly those with a recent cerebrovascular accident or with a cranial trauma). On the other hand, embolic stroke rates may be slightly reduced in patients receiving thrombolytic therapy, perhaps because of infarct size reduction and the anticoagulant effects of thrombolytic agents. Overall, the excess of any stroke (haemorrhagic or embolic) with thrombolytic therapy appears to be small, averaging about four (SD 0·8) per 1000 patients treated in the large studies[12]. About half of these strokes were fatal. Of the survivors about half were moderately or severely disabled while the others experienced little or no disability[43].

A few independent predictors for intracranial haemorrhage were identified by a case control study which included 150 patients with such bleeding and 294 matched controls from various trials. These predictors were age over 65 years, body weight below 70 kg, hypertension (defined as blood pressure greater than 165/95 mmHg) on hospital admission and the use of alteplase (vs streptokinase)[42]. These findings were supported by analyses of the GUSTO-1 database, which found age (median age of patients without and with haemorrhagic stroke was 61 and 70 years, respectively) and previous cerebrovascular disease to be risk factors for intracranial bleeding (although the latter was an exclusion criterion in the trial)[43].

Even though it is possible to identify subgroups of patients with increased intracranial bleeding risk from observational data, the large randomized trials did not demonstrate a significant excess risk due to thrombolytic therapy in these subgroups[12]. In the FTT analysis, an excess of strokes with thrombolytic therapy occurred during day 0–1, and was mainly due to an increase in intracranial haemorrhage. This early excess appeared to be somewhat greater in patients aged 75 years and above, but it was not significantly greater than in those aged 55–74 years (and strokes were rare among those under 55 years). The excess of all strokes (haemorrhagic and embolic) during the hospital stay was also not strongly related to age, blood pressure or other patient characteristics.

The available evidence, therefore, supports the use of thrombolytic therapy in most patients presenting with ST segment elevation or bundle branch block within 12 h of symptom onset unless a markedly increased bleeding risk can be identified. In each individual patient the likely benefits and risks of thrombolytic therapy should be weighed carefully. But risks should not be exaggerated as this may result in inappropriate under-treatment.

Conclusions

- Thrombolytic therapy carries an increased risk for intracranial haemorrhage, while embolic strokes are slightly reduced. Overall, thrombolytic treatment is associated with about four extra strokes per 1000 patients treated. However, in all categories of patients presenting with ST segment elevation or

bundle branch block within 12 h that have been studied, the survival benefits of thrombolytic therapy outweigh the risks.

- Advanced age, a history of cerebrovascular disease, low body weight, hypertension on hospital admission as well as a recent head trauma are important risk factors for the occurrence of intracranial bleeding complications. However, the excess risk of early strokes (mainly intracranial haemorrhage) or of total strokes due to thrombolysis are not strongly related to age, blood pressure or other patient characteristics.

7. Commonly used modes of reperfusion therapy in clinical practice include different thrombolytic regimens with streptokinase or (accelerated) tissue plasminogen activator, and direct angioplasty. What is the relationship between survival benefits, cerebral bleeding risks and costs for these three options? Comparisons of different thrombolytic regimens

Different thrombolytic regimens, whether based on streptokinase, (accelerated) recombinant tissue plasminogen activator or anisoylated plasminogen streptokinase activator complex (APSAC), have all been shown to produce substantial improvements in survival. There was no agreement, however, as to whether there was any worthwhile net difference in clinical outcome between the different thrombolytic regimens that have been studied.

First viewpoint

Neither the GISSI-2/International trial nor ISIS-3 found a survival difference between streptokinase (1·5 MU infused over 1 h, either with or without subcutaneous heparin) or tissue plasminogen activator (alteplase/duteplase infused over 3 to 4 h, also with or without heparin)[39,44,45]. The GUSTO-1 investigators, however, reported a significant reduction in 30-day mortality of 10 (SD 3) per 1000 patients treated with *accelerated* administered tissue plasminogen activator (alteplase infused over 1·5 h, combined with intravenous heparin) compared with the standard streptokinase regimen (either with subcutaneous or intravenous heparin)[46]. This benefit was maintained for at least 1 year[47], and was observed in almost all subgroups, including elderly patients, and those presenting after 3 h. Some questions have been raised about supposed differences in outcome between U.S. and non-U.S. patients, but these non-significant differences could largely be explained by differences in baseline characteristics between patients enrolled in these two continents[48].

The risk of non-fatal stroke (especially of intracranial haemorrhage) is increased with tissue plasminogen activator compared with streptokinase. In GUSTO-1, a significant absolute increase in total stroke was reported of 2·6 (SD 1·5) per 1000 patients treated with accelerated tissue plasminogen activator. Nevertheless, the absolute net clinical benefit, of the combined end point of 30-day mortality or non-fatal stroke was still nine (SD 3) patients per 1000 treated with accelerated tissue plasminogen activator. Thus, *accelerated* tissue plasminogen activator has been shown to be clearly superior to streptokinase.

In spite of the favourable outcome with accelerated tissue plasminogen activator, application in clinical practice remains limited by the relative high costs. A cost-effectiveness study of the GUSTO data estimated the additional costs of accelerated tissue plasminogen activator compared with streptokinase at $27 369 per life year added, based on the cost of tissue plasminogen activator in the U.S.[49]. Accordingly, accelerated tissue plasminogen activator was recommended in patients who might benefit greatly from reperfusion therapy, i.e. those with a high mortality risk without thrombolysis[18].

Second viewpoint

In contrast with this first view, it was argued that, when the totality of the clinical trial evidence is considered, there is no good evidence that any particular thrombolytic regimen is clearly better. More intensive regimens, generally based on tissue plasminogen activator, do not increase the overall proportion of arteries eventually opened within the first few hours, but they did work slightly more rapidly. Although opening the arteries half an hour or one hour earlier should produce some cardiac benefit, the fundamental question is whether any cardiovascular advantages from more intensive thrombolytic regimens outweigh any cerebrovascular disadvantages.

In the three large trials of the standard 1 h 1·5 MU streptokinase regimen vs tissue plasminogen activator-based fibrinolytic regimens, patients were entered on average about 2–3 h after the onset of symptoms in GISSI-2, 4 h in ISIS-3 and 2 h in GUSTO-1[39,44,46]. In each, the tissue plasminogen activator-based regimens were designed to ensure appreciably better 90-min coronary artery patency than the standard streptokinase regimen with which

they were compared, and the accompanying dose of aspirin was sufficiently large to contribute substantially towards the maintenance of that early patency. Moreover, both of the tissue plasminogen activator-based regimens in GUSTO-1 were very similar to each other in terms of the total dose given in the first hour (82 mg of alteplase with the accelerated tissue plasminogen activator-alone regimen and 78 mg of alteplase with the other tissue plasminogen activator-based regimen) and in terms of 90-min TIMI 2/3 patency. Hence, it is most appropriate — in order to avoid selective emphasis on particular trial results — to consider all three trials together[50].

Overall in these trials, there was a highly significant excess of 3·3 (SD 0·8) strokes per 1000 treated with tissue plasminogen activator compared with streptokinase[50]. Most of this excess occurred within the first day of giving tissue plasminogen activator, and was attributed to an even more definite excess of 2·9 (SD 0·5) cerebral haemorrhages per 1000. These excesses with the tissue plasminogen activator regimens increased with increasing age and blood pressure. Overall, the tissue plasminogen activator-based regimens were associated with 4·9 (SD 1·8) fewer non-stroke deaths per 1000 compared with streptokinase, but the 95% confidence interval for this estimate spans a wide range from about one to about nine fewer non-stroke deaths per 1000. When taken all together, the directly randomized comparisons suggest such tissue plasminogen activator-based regimens might confer a non-significant improvement of only one or two per 1000 in net clinical outcome. But, whereas the hazard is definite (about three additional cerebral haemorrhages per 1000) any excess of benefit over hazard is uncertain.

Comparison of thrombolytic therapy versus primary angioplasty

Preliminary results from a pooled analysis of data from three small trials of thrombolytic therapy (405 patients; 256 tissue plasminogen activator and 149 streptokinase) vs angioplasty (394 patients) indicated a favourable outcome with the latter strategy (6·4% vs 2·6% in-hospital mortality; reduction of 39 per 1000, with a 95% confidence interval of 10 to 68, $P=0·01$)[7,51–54]. This apparent mortality advantage of primary angioplasty was observed largely among patients at somewhat higher risk (elderly, anterior infarction, increased heart rate) and appeared to be associated with fewer strokes, although these apparent benefits are uncertain due to the small numbers of patients studied in these trials. In the recently completed larger (n=1138) GUSTO-2b substudy of accelerated tissue plasminogen activator vs direct angioplasty, however, the observed differences in survival were less striking: 30-day mortality was 5·7% in the direct percutaneous transluminal coronary angioplasty group vs 7·0% in thrombolytic-treated patients (a non-significant difference with a 95% confidence interval of 15 more to 40 fewer deaths per 1000 angioplasties). The combined 30-day endpoint of death, re-infarction or disabling stroke was significantly lower in patients treated with direct percutaneous transluminal coronary angioplasty (9·6%) compared with thrombolytic therapy (13·7%; reduction of 41 per 1000, but with 95% confidence interval of 3 to 78, $P=0·033$)[55].

The initial costs of an angioplasty procedure are relatively high. However, some of these costs may be offset during follow-up. Costs after thrombolytic therapy may be higher, due to a higher number of interventions and re-admissions[56].

Conclusions

- Any differences in outcome between reperfusion strategies are likely to be small in comparison with the differences in outcome between reperfusion therapy and no reperfusion therapy. Hence, most emphasis should be on ensuring that eligible patients receive some effective reperfusion therapy as rapidly as is practicable without worrying overmuch about which strategy to choose.
- Tissue plasminogen activator-based therapy produces a higher rate of early coronary patency and, probably, some improvement in cardiac mortality. On the other hand, treatment with tissue plasminogen activator is associated with a greater risk of early intracranial haemorrhage compared with the 'standard' streptokinase regimen. The balance of advantages (survival) and disadvantages (cerebral bleeding) with tissue plasminogen activator is judged differently. Some investigators are convinced that the use of accelerated alteplase with intravenous heparin yields a significant net clinical benefit over streptokinase, while others consider that whereas the hazard with tissue plasminogen activator is definite any excess of benefit over hazard is uncertain.
- Direct angioplasty may be more effective at reducing mortality than thrombolytic therapy, although the current estimates of benefit are uncertain due to the relatively small number of randomized patients studied. Primary angioplasty may be offered as an alternative to thrombolytic therapy in centres with

adequate facilities and experience, particularly in patients with large infarcts and increased cerebral bleeding risk.

- Additional much larger studies are needed to compare the (cost)-efficacy of direct angioplasty and thrombolytic therapy reliably.

8. How can the benefits, risks and costs of different reperfusion strategies be integrated into clinical decision making?

In clinical practice a physician must choose for each individual patient between different therapies with different costs and efficacy. This choice is often restricted by limited resources or organizational constraints (e.g. availability of direct angioplasty). Since the effect of reperfusion therapy is strongly related to treatment delay, in the acute setting there is little time in which to weigh up the potential benefits and risks of different treatment regimens in an individual patient. In this situation, a treatment protocol may be a powerful tool to help rapid decision-making in a consistent manner, although this cannot replace the physician's clinical impression of the patient.

A range of treatment guidelines for individual patients has been developed. Ideally such protocols would first provide reliable estimates of the expected treatment benefit, for example the gain in one year survival, based on a limited number of relevant individual characteristics (such as the duration of symptoms, age and ECG changes). Secondly, a reliable estimate of the patient's (cerebral bleeding) risk from treatment would be estimated. Finally, benefits and risks would be weighed, and advice given on whether or not to use reperfusion therapy and possibly on the choice of therapy. Such reperfusion treatment protocols might be presented on simple paper charts, or might involve the assistance of a computer program[18,20,57–62].

Conclusions

- A reliable reperfusion treatment protocol may be a powerful tool to assist in the optimal and consistent treatment of acute myocardial infarction patients.
- Protocols need to be evaluated, improved and extended. Analysis of large databases from clinical trials, as well as from prospective studies and registries in clinical practice, would help in this task.

Future directions

The introduction of reperfusion therapy has considerably improved the prognosis of patients with evolving myocardial infarction during the last decade. Mortality at 1 month has been reduced by approximately 30 deaths per 1000 patients treated within 6 h from symptom onset, despite a small excess of cerebral bleeding complications (approximately four per 1000).

Analysis of existing trial data has shown that the absolute benefit of reperfusion therapy is largely dependent on the patient's baseline mortality risk and the time elapsed from onset of symptoms. Therefore, future investigations should concentrate on:

- *early* initiation of thrombolytic therapy and further evaluation of the effectiveness and costs of prehospital thrombolytic treatment;
- evaluation of the effects of thrombolytic therapy in those patient *subgroups* for which uncertainty about clinical benefit exists (e.g. those presenting after 12 h from symptom onset and those without ST elevation or bundle branch block);
- development of better thrombolytic regimes, that produce coronary patency *rapidly* without increasing the risk of cerebral haemorrhage (e.g. combination of thrombolytic drugs and powerful anti-thrombotic agents, such as the GP IIb/IIa receptor blockers);
- evaluation of the effects of newer antithrombotics on *sustained* patency;
- study of the *mechanisms* of the early mortality associated with thrombolytic therapy and of ways to avoid it;
- further analysis of primary percutaneous transluminal coronary angioplasty (perhaps in combination with coronary stenting) as an *alternative* for thrombolytic therapy.

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THE REPERFUSION THERAPY CONSENSUS GROUP (SEE APPENDIX)

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Appendix

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